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ARGENTAFFIN TUMORS OF THE GASTROINTESTINAL TRACT

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MADISON, WIS.

The literature describing cases of argentaffin tumor of the gastrointestinal tract has become extensive and includes recent complete reviews by Ariel[1] and Dangremond.[2] While there are many reports of the metastasis of argentaffin tumors, the metastasis varying from a local involvement of the mesentery and mesenteric lymph nodes to widely disseminated growths, careful search of the literature reveals reports of only 4 cases of metastasis to the spleen. The following case with multiple microscopic metastases in the spleen is therefore presented, together with a tabular summary of the cases of argentaffin tumor encountered in the postmortem series of the Wisconsin General Hospital.

REPORT OF A CASE

A white woman 58 years old was admitted to the medical service complaining of pain in the stomach and diarrhea. Until the onset of these symptoms, about nine months before admission, she had considered herself well. The diarrhea was accompanied at first by severe abdominal cramps, which subsided in a few days, to be replaced by a dull ache and a feeling of fulness in the abdomen, especially severe about an hour after meals. The frequent stools were light in color and often foamy, and contained undigested food. The diarrhea varied in severity throughout the course. Since the onset of symptoms the patient had lost 22 pounds (10 Kg.). Other complaints were precordial pain and dyspnea on exertion and occasional spells of faintness and weakness. The remainder of the history was noncontributory except for rheumatic fever at the age of 14.

Examination revealed a malnourished white woman, who appeared chronically ill and showed evidence of recent loss of weight. The left cardiac border extended 7 cm. from the midsternal line, and a presystolic rumble and a systolic murmur were heard over the mitral area. The blood pressure was 124 systolic and 82 diastolic. The abdomen was tense and tender, with shifting dulness. The liver extended 12 cm. below the right costal border and into the left upper quadrant and was irregularly nodular.

Laboratory examinations were noncontributory except for a strongly positive guaiac test for blood in the stools.

Roentgenographic examination of the abdomen revealed a calcified myoma of the uterus, downward displacement of the right kidney and enlargement of the liver. Complete studies of the gastrointestinal tract revealed no abnormalities.

The clinical diagnosis was metastatic carcinoma of the liver, primary site undetermined, and rheumatic heart disease with mitral stenosis.

The patient became progressively worse and died on the twelfth day following her admission to the hospital.

The postmortem examination was made one hour after death. The relevant observations follow:

The pulmonic and mitral valves were thickened and stenotic.

In the ileum, about 20 cm. above the ileocecal valve there was a neoplasm which had extended into the mesentery and caused numerous intestinal loops to become adherent in this region. The mesenteric blood vessels had been compressed by the neoplastitc process. The resulting necrosis obscured the picture and made the actual extent of the tumor in the ileum difficult to ascertain grossly. The intestine distal to this area contained tarry feces and the mucosa was hemorrhagic.

Small neoplastic nodules were scattered over the peritoneal surfaces, especially in the lower part of the abdomen and in the pelvis.

The spleen weighed 150 Gm. and was grossly normal in appearance.

The liver weighed 1,850 Gm. Its surface was studded with a large number of neoplastic nodules varying from a few millimeters to 3 or 4 cm. in diameter. These were pale in color with depressed hemorrhagic centers. Several larger nodules were dark in color and fluctuant. Section revealed the entire right lobe to be filled with masses of neoplastic tissue with cystic centers containing blood and necrotic material. The largest of these cysts measured 5 cm. in diameter, and others ranged from 1 to 4 cm. in diameter. The entire caudate lobe of the liver was replaced by a mass of friable necrotic hemorrhagic material with a cystic center containing fluid blood.

The uterus contained a large calcified myoma.

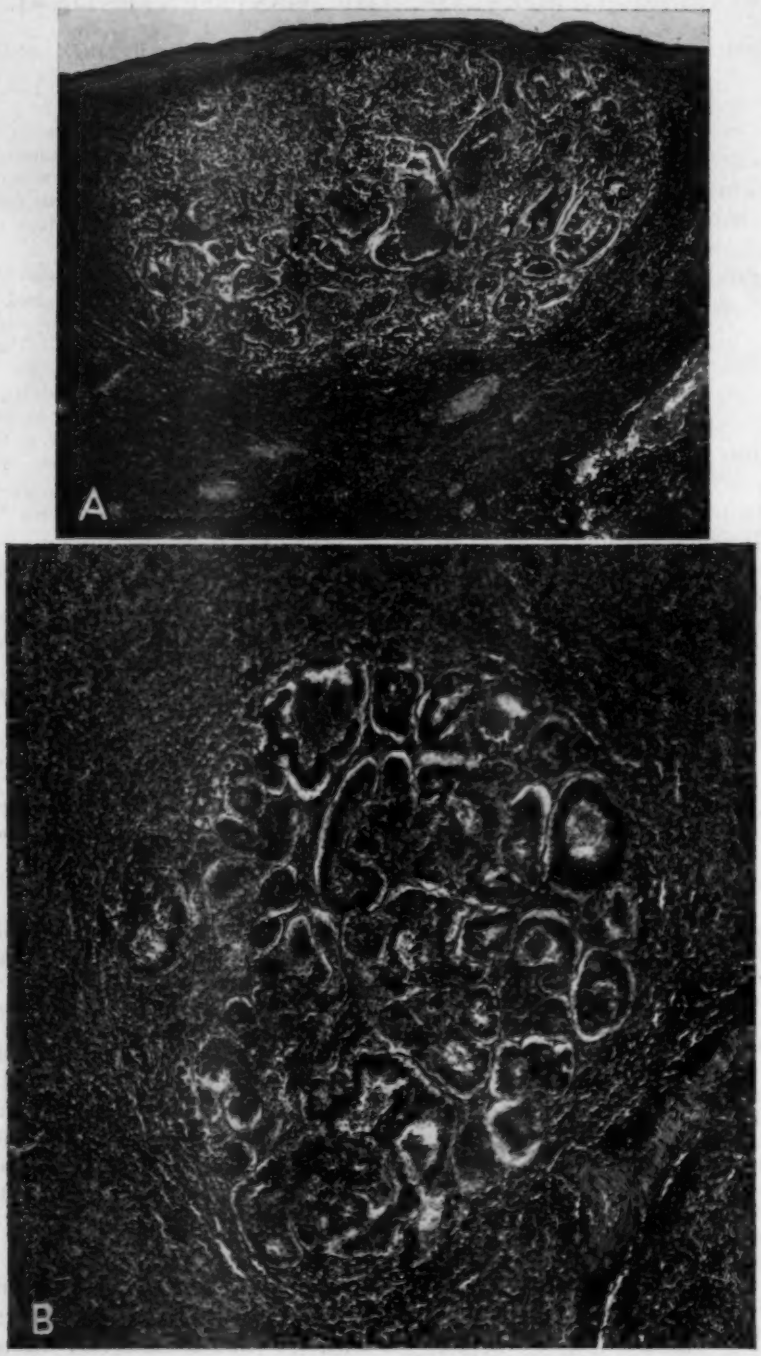
Microscopic examination revealed a typical argentaffin tumor primary in the ileum with metastases in the mesentery, the mesenteric lymph nodes, the wall of the gallbladder, the liver, the spleen and the peritoneal surfaces. From these peritoneal implants there was invasion of both ovaries and the wall of the descending colon. The splenic metastases were microscopic in size. One was found just beneath the capsule (*A* in figure) and several in the deeper portions of the parenchyma (*B*). One small artery was filled with tumor cells.

COMMENT

The early workers in describing argentaffin tumor of the gastrointestinal tract were impressed with its clinical innocence despite a cancerous appearance in some cases. Bunting[3] in 1904 called attention to a general similarity in behavior to Krompecher's basal cell carcinoma of the skin, differentiated the argentaffin tumor from adenocarcinoma of the gastrointestinal tract and cited

From the Department of Pathology, University of Wisconsin.

1. Ariel, I. M.: Arch. Path. **27**:25, 1939.
2. Dangremond, G.: Am. J. Clin. Path. **12**:223, 1942.
3. Bunting, C. H.: Bull. Johns Hopkins Hosp. **5**: 389, 1904.



Sections of splenic metastases of an argentaffin tumor primary in the ileum: *A*, subcapsular nodule in the spleen (hematoxylin and eosin stain; × 50). *B*, deep nodule in the spleen (hematoxylin and eosin stain; × 100).

a similar tumor reported by Ransom [4] in 1890 which had metastasized to the liver. For some years following this work, the argentaffin tumor was considered noncancerous, and the infrequent reports in the literature listed no cases with metastases. Gradually, scattered reports of cases of argentaffin tumor that had metastasized began to appear. Forbus [5] in 1925 and Cooke [6] in 1931 reviewed the subject and summarized the reported cases of metastasizing argentaffin tumor. The latter author collected 115 cases, in 21 of which the tumor had metastasized—an incidence of 18 per cent. Ariel [1] in 1939 summarized all cases reported and found a total of 237, in 59 of which the tumor had metastasized, an incidence of 24.9 per cent. Dangremond [2] in 1942 reviewed the literature and stated that of 283 cases of argentaffin tumor, 106 were cases in which metastasis had occurred—an incidence of 37.4 per cent. Harville [7] found 6 cases of argentaffin tumor in the records of the Vancouver General Hospital, in 2 of which the tumor had metastasized to the mesenteric lymph glands. Dockerty and Ashburn [8] in 1943 reported 13 additional cases of cancerous argentaffin tumor in a total of 30 cases. Gold and Grayzel [9] in 1943 reported a case of cancerous argentaffin tumor in which there was metastasis to the liver. Potter and Docter [10] in 1944 reported a case of argentaffin tumor of the cecum with metastasis to the regional lymph nodes and to the liver, thus bringing the total number of cases of argentaffin tumor reported to date to 321, in 123 of which the tumor had metastasized. The incidence of metastasis in the total number of reported cases thus is 38.3 per cent.

Argentaffin Tumors in the Autopsy Series of the State of Wisconsin General Hospital

Autopsy Number	Age	Sex	Location of Tumor	Symptoms	Location of Metastases	Comment
27:10	51	Female	Ileum	Obstruction	Liver-mesentery	
28:50	56	Female	Duodenum	None	None	
28:57	71	Female	Ileum	Obstruction	None	
33:39	22	Male	Appendix	None	None	
36:39	42	Male	Ileum	None	None	
37:275	57	Male	Ileum	None	None	Multiple
42:121	55	Male	Ileum	None	None	Multiple
42:205	72	Male	Ileum	Obstruction	Mesenteric nodes	
43:34	74	Male	Ileum	None	None	
43:73	54	Male	Appendix	None	None	
44:29	58	Female	Ileum	Melena, diarrhea, abdominal pain, loss of weight	Mesentery, mesenteric nodes, peritoneal surface of colon, uterus, ovaries, liver, spleen, gallbladder	

It must be noted that the term "metastasis" as applied in the literature varies rather widely in meaning, since a tumor is classified as metastasizing by some if the muscle coat and the mesentery are invaded. Consequently the percentage given includes many instances in which the metastases are not distant or hematogenous.

In the series of 11 cases of argentaffin tumor encountered in the postmortem series of the Wisconsin General Hospital 3 are classed as cases of metastasizing tumor (table). In the first the mesentery and the mesenteric lymph nodes were invaded, in the second both the mesentery and the liver were involved, and in the third, which is the case reported here, widespread abdominal metastases were found. The incidence of metastasizing argentaffin tumor in our series is 27.2 per cent. These cases bring the total number of cases of argentaffin tumor reported to date to 332, in 126 of which the neoplasm metastasized—an incidence of 37.9 per cent.

The increase in the percentage of cases of metastasizing argentaffin tumor from the 18 per cent reported by Cooke in 1931 to the present 37.9 per cent reflects increasing interest in this type of tumor both from the pathologic and from the clinical standpoint. More attention has been given recently to antemortem diagnosis, since the growth characteristics should permit surgical removal of the nonmetastasizing forms.

As previously stated, cases of argentaffin tumor metastasizing to the spleen are uncommon. In the 2 cases reported by Selberg [11] in 1940 the splenic metastases were unquestionably of hematogenous origin, as neoplastic cells were found deep in the splenic pulp. The involvement of the spleen in the case reported by Hagemann [12] in 1919, although associated with metastases in other organs, appeared to be a simple extension of the tumor to the region of the hilus of the spleen. In Aalkjaer's [13] case, reported in 1937, the lesion

4. Ransom, W. B.: Lancet **2**:1020, 1890.

5. Forbus, W. D.: Bull. Johns Hopkins Hosp. **37**: 130, 1925.

6. Cooke, H. H.: Arch. Surg. **22**:568, 1931.

7. Harville, L. B.: Bull. Vancouver M. A. **19**:17, 1942.

8. Dockerty, M. B., and Ashburn, F. S.: Arch. Surg. **47**:221, 1943; abstracted, Proc. Staff Meet., Mayo Clin. **19**:228, 1944.

9. Gold, I. R., and Grayzel, D. M.: Am. J. Surg. **60**:144, 1943.

10. Potter, E. B., and Docter, J. M.: Am. J. Path. **28**:143, 1944.

11. Selberg, W.: Virchows Arch. f. path. Anat. **306**:467, 1940.

12. Hagemann, F.: Ztschr. f. Krebsforsch. **16**:404, 1919.

13. Aalkjaer, V.: Lyon chir. **34**:542, 1937.

was a peritoneal implant with invasion of the splenic capsule rather than a true hematogenous metastasis. With the exclusion of these 2 cases, there remain only 2 reported cases of hematogenous involvement of the spleen by a metastasizing argentaffin tumor. The case reported here is included in this category since tumor nodules were found deep in the splenic substance.

The metastatic lesions in the liver in this case resemble that described by Gold and Grayzel,[9] who reported a case of argentaffin tumor primary in the ileum with a large hepatic metastasis, the central portion of which was necrotic and hemorrhagic. A "liver abscess" had been drained surgically some years before death, and this in the authors' opinion may actually have been a tumor nodule which had undergone softening. In our case sections through the right lobe of the liver revealed almost complete replacement of liver tissue by neoplastic masses with cystic centers containing blood and necrotic material. The largest of these cysts measured 5 cm. in diameter, and others ranged from 1 to 4 cm. in diameter. The entire caudate lobe of the liver was replaced by a mass of friable necrotic hemorrhagic material with a cystic center containing fluid blood.

The clinical findings associated with these tumors are variable. Partial or complete obstruction of the small intestine caused by kinking and adherence of loops of intestine at or about the site of the tumor has formed a prominent part of the clinical picture in many cases. Cooke [6] cited 115 cases of argentaffin tumor, in 17.4 per cent of which symptoms of obstruction were produced. In our series of 11 cases clinical evidence of obstruction was present in 3. When symptoms of obstruction are not present, as in the majority of cases of argentaffin tumor, the clinical picture is often indefinite. In most cases of cancerous argentaffin tumor the symptoms do not point to the location of the primary lesion; the general clinical picture is that of cancer with specific evidence of metastases, most commonly in the liver. A frequent clinical impression in these cases is "metastatic carcinoma of the liver, primary site undetermined."

Miller and Hermann [14] in 1942 called attention to this aspect of the problem and proposed a method of roentgenographic recognition of these lesions. They stated that "the roentgen findings of tumor at a point of kinking and partial obstruction of the small bowel is believed to be a highly suggestive sign of these tumors." This suggestion offers little aid in cases in which there are no symptoms or signs of partial intestinal obstruction, as in the case reported here.

Blood in the stools as determined by common laboratory procedures has been considered by most authors to be an infrequent finding in cases of argentaffin tumor of the small intestine. Miller and Hermann [14] stated that the guaiac test is usually negative since the argentaffin tumor does not ulcerate or bleed. Dangremond [2] observed that melena, usually present with carcinoma of the intestine, is not a common symptom of the argentaffin tumor unless there is ulceration, but did not describe any such lesion in his series. Gold and Grayzel [9] mentioned the appearance of occult blood in the stools on two occasions during their patient's final stay in the hospital but their autopsy report does not mention necrosis, ulceration of the tumor nodules or any interruption of the blood supply to the ileum. There is no description of the contents of the intestine below the lesion. In the case reported here the only pertinent laboratory sign was blood in the stools as determined by the guaiac test. The origin of the melena in this case could not be definitely ascribed to ulceration of the tumor, as the gross picture of the initial lesion was obscured by the marked necrosis of the involved segment of ileum. The appearance of blood in the stools may have been the result of this necrosis in spite of the fact that roentgenographic studies of the intestine made two days prior to death were reported as demonstrating no lesion. It is probable that the vascular occlusion caused by extension of the tumor was a gradual process with slowly extending necrosis. This phenomenon would explain the fact that the blood in the stools, detectable only by chemical means at first, increased until at the time of autopsy a large amount of tarry feces was present below the site of the lesion.

Diarrhea is not an infrequent finding in cases of argentaffin tumor of the small intestine but is of no specific diagnostic value unless the stools are observed to contain blood.

The term "carcinoid" was proposed for this type of tumor in 1907 by Oberndorfer,[15] who thought at that time that it was entirely noncancerous. The discovery that the tumor was derived from the argentaffin cells of the gastrointestinal tract by Gosset and Masson [16] and further investigation by Masson [17] led to the designation "argentaffin tumor." The increasing number of reported cases with metastases has established the tumor as true carcinoma and has

14. Miller, E. R., and Hermann, W. W.: Radiology **39**:214, 1942.

15. Oberndorfer, S.: Frankfurt. Ztschr. f. Path. **1**: 426, 1907.

16. Gosset, A., and Masson, P.: Presse méd. **22**:237, 1914.

17. Masson, P.: Am. J. Path. **4**:181, 1928.

made the term "carcinoid" obsolete. Mayo and Wilson [18] in 1941 considered the tumor as true carcinoma, and in subsequent publications Dockerty and Ashburn,[8] Hopping, Dockerty and Masson [19] and Pennington and Priestly [20] have classified it as "adenocarcinoma grade 1 malignancy of the carcinoid type," as distinguished from "ordinary adenocarcinoma." It seems logical to discard the meaningless term "carcinoid." It is proposed, therefore, that this type of tumor shall be designated "argentaffin carcinoma" or "benign argentaffin tumor" according to whether it shows cancerous properties or not.

18. Mayo, C. W., and Wilson, W. D.: Minnesota Med. **24**:178, 1941.

19. Hopping, R. A.; Dockerty, M. B., and Masson, J. C.: Arch. Surg. **45**:613, 1942.

20. Pennington, R. E., and Priestly, J. T.: Proc. Staff Meet., Mayo Clin. **18**:49, 1943.

SUMMARY

The case of argentaffin carcinoma of the ileum with hematogenous metastasis to the spleen presented is the third such case to be reported. There were also metastases of an unusual type in the liver. Among the cases of argentaffin tumor encountered in the autopsy series of the Wisconsin General Hospital the incidence of cases with metastasis is 27.2 per cent, compared with 37.9 per cent in the literature.

The clinical diagnosis of argentaffin tumor is of great importance since the proportion of cases in which the tumor is noncancerous is high and surgical treatment therefore offers a good prognosis.

It is proposed that the term "carcinoid" be discarded and the terms "benign argentaffin tumor" and "argentaffin carcinoma" be used.

PSEUDOCARCINOMATOUS HYPERPLASIA IN PRIMARY, SECONDARY AND TERTIARY CUTANEOUS SYPHILIS

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The occurrence of pseudocarcinomatous hyperplasia in cutaneous lesions of syphilis may mislead the pathologist into making a report of carcinoma and in turn be responsible for misdirecting the clinician into treating his patient for carcinoma instead of syphilis. This is likely to occur most frequently in cases of pseudocarcinomatous hyperplasia superimposed on a gumma. Extragenital primary syphilis with pseudocarcinomatous hyperplasia may also be confused with carcinoma, particularly because of the frequency with which the former occurs at carcinoma-bearing sites. Occasionally a solitary lesion of late secondary syphilis or of precocious benign tertiary syphilis will also present this diagnostic problem.

Too frequently is a carcinomatous-looking lesion of the skin or the mucous membrane removed surgically or irradiated without the possibility of syphilis entering the clinician's mind and without a serologic test for syphilis being performed. This omission is particularly important in the presence of a lesion of the face, lip, tongue, vulva or cervix.

The clinician has come to recognize the importance of the biopsy and to appreciate the difficulty of differentiating carcinoma of skin or of mucous membrane from certain manifestations of syphilis merely on their gross morphologic features. As a result, the clinician relies heavily on the histologic observations and consciously or subconsciously passes the final responsibility for the diagnosis on to the pathologist. The latter, without the advantage of the clinician's knowledge of the case (usually because he is not given any or at most a sketchy and inadequate history) is forced to make a diagnosis based on histologic criteria, which are often not conclusive in themselves. If a positive serologic report is submitted to the pathologist with the tissue, he has that additional clue to assist his interpretation of the histologic observations. Too often no such report is given the pathologist, or the patient is one of that group of syphilitic patients whose serologic tests are negative.

The material for this paper was collected at the Los Angeles County Hospital, 1942.

Reports of the "cure of cutaneous carcinoma" in a syphilitic patient with antisyphilitic therapy are illustrations of the mistaking of the histologic features of pseudocarcinomatous hyperplasia superimposed on cutaneous syphilis for carcinoma.

Touraine [1] reported such a "cure" in a patient with late latent syphilis in whom an ulcer developed in the inner canthus area of the left eye. The biopsy was reported by Civatte, who made a diagnosis of squamous cell carcinoma on the basis of invasive epithelial proliferation, many mitoses and dyskeratosis. This diagnosis was accepted by Touraine, and the patient was treated by a series of injections of a mercury compound and neoarsphenamine, after two months of which the lesion healed completely. His explanation for starting this type of treatment is that he and Solente [2] had previously noted the cure of a cutaneous "carcinoma" appearing in a syphilitic patient during the course of the latter's antisyphilitic treatment. It seems likely that in both of these cases the lesion actually was gumma with pseudocarcinomatous hyperplasia.

Marin and Bernier [3] reported the case of a patient known to be syphilitic in whom serpiginous ulcerations developed about both corners of the mouth. The histologic report described thick masses of epithelial strands and lobules containing many mitotic figures and monstrous cells penetrating the cutis, which were embedded in a granulomatous infiltrate packed with plasma cells. From these observations they concluded that they were dealing with carcinoma of the squamous cell type and were not dissuaded from this concept when the lesions healed rapidly with antisyphilitic therapy. The histologic section from the involved area in this case does reveal epithelial proliferation of intense activity. The cytologic features, however, are not incompatible with pseudocarcinomatous hyperplasia which has

1. Touraine, A.: Bull. Soc. franç. de dermat. et syph. **44**:1986, 1937.

2. Touraine, A., and Solente: Bull. Soc. franç. de dermat. et syph. **42**:415, 1935.

3. Marin, A., and Bernier, A.: Bull. Soc. franç. de dermat. et syph. **45**:463, 1938.

become superimposed on a cutaneous lesion of syphilis.

The criteria established for cancer by Broders [4] refer to the altered characteristics of the individual cell, i. e., irregularity of size and shape, increased size and number of nucleoli, alteration of the ratio of the size of the nucleus to that of the cytoplasm, atypical mitosis and other changes.

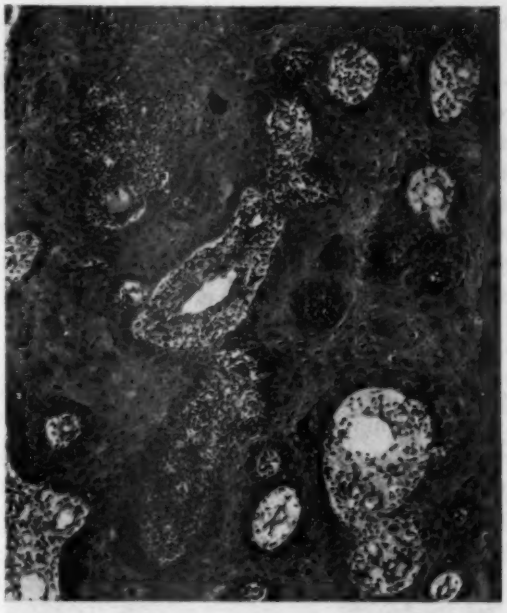

Fig. 1.—Section of the biopsy specimen taken from the lesion in case 1. Acanthosis suggested carcinoma of grade 1. The lesion was then removed by cautery.

Epithelial proliferation with penetration into the corium is too often assumed to constitute conclusive evidence of cancer. Rather, this feature should be regarded as coincidental with cancer.

Pseudocarcinomatous hyperplasia cannot always be easily differentiated histologically from carcinoma. In the former Broders [4] emphasized the absence of the features of the individual cell of cancer. Montgomery and Holman [5] cited the importance of the normal arrangement of the cells in pseudocarcinomatous hyperplasia, as well as the absence of the features of dyskeratosis. In addition, he noted that invasion of the epithelium by inflammatory cells does not occur in carcinoma. Winer [6] stated that edema of the cutis and the epidermis, both intercellular and intracellular, and the retention of the intercellular bridges as well as of the basement membrane, are present in pseudocarcinomatous hyperplasia. In addition, the characteristic infiltrate of the cutis and the changes in the vessels of syphilis are important. When all these criteria are taken into account, however, it may still be difficult to distinguish carcinoma and pseudocarcinomatous hyperplasia by study of the histologic section alone.

The following 3 cases are presented as offering illustrations of pseudocarcinomatous hyperplasia occurring in primary, secondary and tertiary cutaneous syphilis.

CASE 1

An adult Negro had a dollar-sized, raised granulomatous ulcer of the suprapubic region in the midline. The ulcer had started as a small lesion four months before and had steadily increased in size. The biopsy showed intense epithelial proliferation with invasion of the corium and many other cytologic features of cancer. On the basis of these observations and the clinical appearance of the lesion, the diagnosis of squamous cell carcinoma was made. The lesion was then removed with cautery. Sections showed long epithelial strands penetrating deeply into the cutis, almost a pure plasma cell infiltrate between these epithelial strands and

Fig. 2.—Section of the lesion in case 1 after it was removed by cautery. Acanthosis is marked. The infiltrate was found to consist mostly of plasma cells, arousing the suspicion of syphilis. A serologic test for syphilis was positive.

throughout the rest of the cutis, and perivascular cuffing. Staining for spirochetes by the Krajian [7] method revealed typical Treponema pallidum in myriad number. The lesion was finally interpreted as an extragenital chancre with pseudocarcinomatous hyperplasia. Anti-

4. Broders, A. C.: J. A. M. A. **99**:1670, 1932.

5. Montgomery, H., and Holman, J. C., Jr.: Proc. Staff Meet., Mayo Clin. **13**:465, 1938. Montgomery, H., in discussion on Winer.[6]

6. Winer, L. H.: Arch. Dermat. & Syph. **42**:856, 1940.

7. Krajian, A. A.: Arch. Dermat. & Syph. **32**:764, 1935.

syphilitic therapy was begun, during which the cauterized lesion readily healed.

CASE 2

A white man had on the right side of his nose a dull red, firm nodule, measuring 1.5 cm., which had started as a small papule seven weeks before. The diagnosis of primary syphilis (penile chancre) had been made five weeks earlier, for which he had received only four injections, one in the hip and three in the arm. Even with the history of primary syphilis and

Fig. 3.—Section of the biopsy specimen taken from the lesion in case 2 showing invasive epithelial proliferation and plasma cell infiltration. A stain for spirochetes showed T. pallidum. The lesion was interpreted as a late secondary syphilid with pseudocarcinomatous hyperplasia.

positive serologic tests for syphilis, this lesion could not be identified clinically. A biopsy was made, which revealed epithelial strands extending into the midcorium and a plasma cell infiltrate. A Krajian stain revealed an occasional typical T. pallidum. The lesion was then interpreted as a late secondary syphilid, and under antisyphilitic treatment it rapidly involuted.

CASE 3

A white man had a serpiginous noduloulcerative tertiary syphilid surrounding the outer portion of the left eye. The lesion had been present for several years and had long been resistant to treatment. Serologic tests for syphilis were positive. Because of the resistance to treatment, a biopy was made. A granulomatous infiltrate was observed throughout the corium, compatible with gumma, but there were also strands and clumps of epithelial cells that had penetrated the midcorium.

RÉSUMÉ

The lesion in the first case proved to be an extragenital chancre which was originally interpreted as a carcinoma clinically and histologically. The possibility of a chancre was not considered, because of the site of the lesion and because of its looking like a fungating tumor. Even though it was realized that cutaneous carcinoma is unusual in Negroes, the biopsy showed such striking epithelial proliferation, as well as other features suggesting cancer, that little uncertainty was felt about making a diagnosis of carcinoma. Further histologic study of the excised lesion confirmed the impression received from the biopsy. It was only after the serologic test for syphilis was found to be positive and the plasma cell infiltrate reevaluated that the possibility of a chancre was considered. The diagnosis was readily confirmed by the spirochetal stain.

The patient in the second case was known to be syphilitic, but the lesion on the side of the nose was not at first believed to be related to the infection. The epithelial proliferation that was found in the histologic specimen further confused the picture, because the lesion was not carcinoma clinically. On the possibility of the lesion being a late secondary syphilid, staining for spirochetes was done, and the presence of T. pallidum confirmed the diagnosis.

The lesion in the third case was submitted to biopsy because it was thought that superimposed carcinoma might account for the failure of the lesion to respond to treatment. Even though the section showed penetrating epithelial cell groups, there were insufficient histologic criteria for a diagnosis of carcinoma.

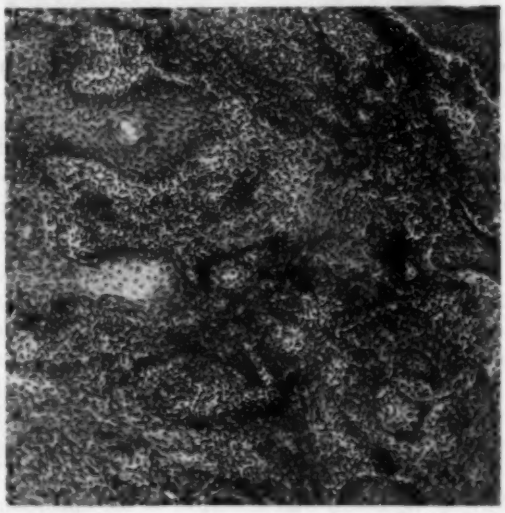

Fig. 4.—Section from the biopsy specimen taken from the syphilid in case 3, showing epithelial proliferation and a granulomatous infiltrate. The possibility of carcinoma was investigated to explain the resistance to treatment and the presence of carcinoma was eliminated. The diagnosis was gumma with pseudocarcinomatous hyperplasia.

COMMENT

It is necessary to be constantly alert to the possibility of pseudocarcinomatous hyperplasia occurring in granulomas and chronic ulcers of

the skin. Some of the many conditions other than cutaneous syphilis in which this hyperplasia occurs are bromoderma, granulomatous mycoses, tuberculosis of the skin, venereal granuloma and chronic ulcers. With some of these the diagnosis can be made conclusively by the identification of the specific etiologic agent. If, however, such a specific agent cannot be found in the search of the specimen, or if none exists, the diagnosis becomes dependent on the histologic structures alone.

It is not always possible to distinguish histologically between pseudocarcinomatous hyperplasia and carcinoma. The former's mimicry of carcinoma of grade 1 or grade 2 frequently is complete and it may even resemble to some extent anaplastic carcinoma. Consequently, the histologist must consider the diagnosis of pseudocarcinomatous hyperplasia in all lesions of the skin showing epithelial proliferation with invasiveness. With every such lesion he should use all the additional laboratory and clinical information that is available in forming his final opinion. It is equally important that the clinician appreciate the limitations of the histologic diagnosis in such cases. The histologic report must be evaluated in terms of the complete clinical picture, and the clinician must assume the final responsibility for the diagnosis.

The particular problem of distinguishing between pseudocarcinomatous hyperplasia and cutaneous manifestations of syphilis is further complicated because of the occasional case in which carcinoma becomes superimposed on tertiary cutaneous syphilis. The clinician must think of this contingency when a gumma fails to respond to adequate antisyphilitic therapy.

SUMMARY

The frequency with which pseudocarcinomatous hyperplasia occurs in cutaneous syphilis is not usually appreciated by the pathologist. It is well for the latter and the clinician to become more aware of this hyperplasia. The clinician then will not "cure" a cutaneous carcinoma with arsenical compounds nor excise and irradiate a syphilid. The histologist will be less apt to call epithelial proliferation carcinoma without eliminating other possibilities.

CONCLUSION

Pseudocarcinomatous hyperplasia occurs in primary, secondary and tertiary cutaneous syphilis. It is frequently difficult to distinguish histologically between this hyperplasia and carcinoma. An adequate history of the case and a report of a serologic test for syphilis should accompany the specimen to the pathologist. The clinician must correlate the gross appearance of the lesion and the history of the case with the histologic observations and assume the final responsibility for the diagnosis.

DIVERTICULA AND DUPLICATIONS OF THE INTESTINAL TRACT

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Under the terms "duplications" or "reduplications," "enteric cysts" or "enterogenic cysts," "ileum duplex" and "giant diverticula" are usually grouped a number of little understood anomalies of the intestinal tract, with the implication that they all arise in the same manner from diverticula of the wall of the gut. For many of them this is the true statement of their embryologic origin, but for others such an origin is obviously impossible, since the anomaly as described could not, starting as a diverticulum, have reached the form and connections ascribed to it by any known embryologic sequence. It is obvious that the group must be subdivided and that some other embryologic origin must be sought in those cases in which the diverticular origin is inadequate. Three articles are available which give a review of this subject: that by Meckel [1] (1882), who was chiefly interested in such structures as anomalies; that by Evans and Keith [2] (1929), who gave a long bibliography and claimed that all arise as diverticula, and the article by Ladd and Gross [3] (1940), who described 18 cases from the Children's Hospital, Boston, and the operative procedures in use there. It is the purpose of the present paper to clarify the current ideas concerning these anomalies and to trace their origins to known conditions in the embryo.

The best known intestinal diverticulum is, of course, that described by Meckel and given his name. It is the occasionally persistent vitelline duct, originally connecting the intestinal tract with the yolk sac, and is normally lost completely before birth. It has its own group of anomalies, such as umbilical fistula or cysts, which are well understood, always recognizable by their position and entirely distinct from the present group.

Other diverticula develop as minute buds from the epithelium of the gut into the subepithelial connective tissue. They were noticed as a constant feature of development by Keibel [4] and by Lewis and Thyng [5] independently in embryos of 20 to 30 mm. (end of second month), chiefly on the antimesenteric surfaces of the intestinal tract. In their formation they resemble somewhat the intestinal glands, although these do not appear until much later. They normally disappear with further growth but exceptionally an individual diverticulum may increase in size, become expanded at the distal end and either remain connected with the lumen by a narrow pedicle or become separated as a closed cyst. By this time the muscle layers of the intestinal wall are well established, so that expansion outward is limited by the inner circular muscle layer and the diverticulum spreads in the looser submucosa (fig. 1 *a*) usually in an aboral direction, as noted by Lewis and Thyng. With further expansion the diverticulum may lift the outer layers to form a bulging protuberance of the intestinal wall; more probably it will bulge inward with increasing expansion, lifting the parent mucosa before it, to form an intraintestinal cyst, which sometimes nearly fills the intestinal lumen. Evans and Keith described such a cyst in the cecum and mentioned cases in which the cyst occurred in the ileum.

The expanding cyst or diverticulum is more likely to find a pathway through the inner muscle layer along one of the clefts by which the vessels make their way to supply the mucosa. Once outside the circular muscles, the cyst can spread in the intermuscular tissue and can lift up the outer muscular layer in the form of a dome (fig. 1 *b*); finally the cyst may pierce the longitudinal muscles also and be covered only by the serosa or the adventitia (figs. 1 *c* and *d*). The presence or the absence of muscle strands in the wall of the cyst indicates which of the methods it has followed. In either case it can then expand freely in the peritoneal or the pleural cavity or in the mediastinal tissue. The right pleural cavity is the one usually invaded, because, since the torsion of the stomach (dorsal wall to the left) is continued along the esophagus for some dis-

From the Department of Anatomy, Harvard Medical School.

1. Meckel, J. H.: Tabulae anatomico-patholigicae, Lipsiae, J. F. Gleditsch, 1882.

2. Evans, A., and Keith, A.: Brit. J. Surg. **17**:34, 1929.

3. Ladd, W. E., and Gross, R. E.: Surg., Gynec. & Obst. **70**:295, 1940.

4. Keibel, F.: Anat. Anz. (supp.) **27**:39, 1905.

5. Lewis, F. T., and Thyng, F. W.: Am. J. Anat. **7**:505, 1908.

tance, the antimesenteric or ventral surface of the latter, along which the diverticulum develops, points slightly to the right. Ladd and Gross have reported 3 cases of diverticulum of this type in the right pleural cavity and mediastinum and probably others along the small intestine.

The type of cyst and diverticulum just described is the only one to which a diverticular origin can properly be assigned. The other types arise from a condition which is normal at a still earlier embryonic stage, through which the intestinal tract has already passed at the time when the minute diverticula first appear. In the embryo of about 6 weeks (10 mm.) the intestinal tract is increasing in length more rapidly than the embryo as a whole and finds room for itself by invading that part of the body cavity which extends into the umbilical cord, forming a normal but temporary umbilical hernia. The acceleration of its rate of growth is initiated or is at least first shown by the cells of its epithelium.

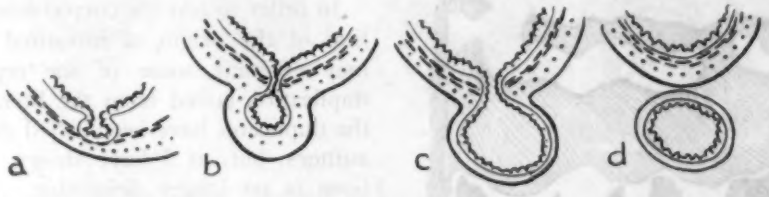

Fig. 1.—Diagrams showing the development of a thin-walled cyst of diverticular origin: (*a*) Diverticulum confined by the circular layer of muscles; it will bulge inward with growth. (*b*) Diverticulum after having pierced the circular layer; the longitudinal layer of muscles bulges outward. (*c*) Diverticulum after both muscular layers have been pierced; the wall of the diverticulum consists of mucosa covered by serosa. (*d*) Free thin-walled cyst.

This is a normal embryologic phenomenon; for instance, the development of the outgrowth which is to form the pancreas is recognizable by a thickening of the epithelial layer at the future position of the outgrowth, before any exterior protrusion is evident, a heaping up of cells locally, as though to provide a reserve of epithelial cells which may be called on to spread and cover the extensive surface about to grow. In the same way the sudden rapid growth in length of the intestinal tract is preceded by an increase of its epithelial cells to such an extent that in certain regions the lumen of the tube becomes much reduced or even occluded (fig. 3 *b*). The latter condition is known as the solid stage of the intestine, or esophagus, or colon, as the case may be. The solid stage never extends throughout the length of the tract at any one time. In different embryos it has been found now here, now there, suggesting that it may pass as a wave of solidification in every embryo or, more probably, that only in certain, variable regions is the increase of epithelium so great as to lead to total occlusion.

If this increase of cells fails to occur in any region of the intestine, the lumen cannot expand properly, and constriction or stenosis of the bowel will result. The rapid lengthening of a local region of the gut in the solid stage may produce a transverse cleft across the mass of epithelial cells and thus allow the ingrowth of the submucosa and even of the muscle layers to cause atresia. In both these anomalies the thickened epithelium acts as an inert mass, which is far from being a usual characteristic.

Normally the cells of the thickened epithelial mass secrete a fluid that gathers into small intercellular droplets, called vacuoles. These are usually arranged in chains or rows lengthwise of the tube and, with individual expansion, may coalesce with each other or with the main lumen. This is shown in the original model by Johnson [6] (fig. 2); on one side of the main lumen the individual vacuoles can be seen, while on the other side several vacuoles have fused with each other and with the main lumen in two places. In normal development, as more and more intervening cells are called away to cover the increasing surface of the growing tube, all the vacuoles finally open into the lumen, become saucer shaped and fade into the general surface. In rare cases the chains of fused vacuoles may retain their form and cause intestinal duplications.

The transition from a single muscular tube enclosing an epithelial core with two parallel lumens to the condition of two more or less separate muscular tubes each with its own epithelial lumen can be followed in the diagrams shown in figure 3 *c*, *d* and *e*. The epithelial cells bordering on the lumens, whether the original lumen or that of a fused chain of vacuoles, become differentiated into columnar cells which, when the underlying undifferentiated cells are called away to cover other parts of the intestine, rest on a prominent basement membrane. As the tube grows in diameter, the two lumens move apart, and the basement membrane comes between them, hugging the bases of the columnar cells. The submucosa follows, and with further separation of the lumens the inner circular muscle layer,

6. Johnson, F. P.: Am. J. Anat. **10**:521, 1910.

the longitudinal muscle and finally the adventitia may follow suit, leading to completely separated intestines, each with its own normal coats. The duplicate intestine thus differs from the diverticulum in that the greater portion of its wall is always provided with all of the normal intestinal layers, since it is a part of the original tube. The fused part of the wall will contain a variable number of layers depending on how far apart the lumens developed.

A chain of vacuoles may coalesce only with each other, or one or more of them may open also into the main lumen, as in Johnson's model. The duplicate may therefore be entirely closed off from the main lumen or may connect with it at either end or anywhere along its length. Sometimes the origin from a chain of vacuoles is indicated by a series of constrictions and bulges. The duplicate may be short, represented merely by a vertically placed bridgelike band across the

Fig. 2.—Sketch of Johnson's model of the epithelium of the esophagus at the seventh week. The epithelial walls have greatly thickened. Below the main lumen are individual vacuoles within the epithelium; above the lumen is a chain of confluent vacuoles, with two orifices.

lumen from one wall to the other [6a] or by a short side loop of the lumen within the submucosa, like that noted by Fischer [7] in the esophagus and called by him "fistula oesophago-oesophagealis." On the other hand, it may be long, even up to 2 or 3 feet (60 to 90 cm.) or more. At first sight it may seem impossible that such a long structure could be developed from a chain of minute vacuoles, but if one realizes that the length of the small intestine when the vacuoles first appear is from 2 to 2.5 mm., whereas at birth the same intestine has attained a length of 2 to 3 meters, and that a duplicate being an integral portion of the intestine must share in this rapid growth, the lengths reported are not especially remarkable.

The minute diverticula are usually found on the antimesenteric surfaces of the intestinal tract, while the duplicates lie between the layers of the mesentery. The reason for the latter position is not at all clear, for in the younger embryos the vacuoles may be seen on all sides of the lumen, apparently scattered at random. Variants are frequently encountered; the duplicate tube may be asymmetric, bulging from one side of the mesentery, or may lie side by side with the main tube, in which case the two tubes may separate completely and the mesentery be split in two, each part of the divided intestine having its own mesentery (fig. 3 *f* and *g*). This result could hardly be reached by a diverticulum growing from the antimesenteric surface of the intestine.

In order to test the correctness of this description of the origin of intestinal duplicates, one may examine some of the reported cases of duplication culled from the literature. Most of the duplicates have been called diverticula by the authors, but, as I have shown, the use of this term is no longer defensible. In the simplest type (fig. 4, *1* to *4*, from Fitz,[8] Evans and Keith,[2] Roth [9] and Poncher and Miller,[10] respectively) the duplicates are not more than a foot long, are closely attached to the intestine for most of their length by the fused circular muscle layers and are of about the same caliber as the main lumen, "like a double-barreled gun." The two lumens may be entirely separate or may join at the oral or the aboral end, or along the midarea, or by two openings or mouths as in Johnson's model of the embryonic esophagus. A second type (fig. 4 *5* and *6*, from Edwards [11] and Kimpton and Crane [12]), obviously closely related to the first, is much longer and characterized by being in part entirely free from the intestine and lying between the layers of the mesentery. Edwards' case is especially interesting as showing that the duplicate intestine is in no way connected with Meckel's diverticulum, as was once maintained, for the short stump of the diverticulum is shown on the antimesenteric surface of the same portion of the intestine which has produced

6a. In a study of some 50 human embryos in the Harvard Embryological Collection I have seen 2 instances of the fused basement membranes and 1 instance of the submucosa intervening between two lumens for a few sections. In the first 2 the duplicate might have been later resorbed into the intestinal mucosa; in the last the intervention would probably have resulted in a bridgelike band.

7. Fischer, W.: Speiseröhre, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926.

8. Fitz, R. H.: Am. J. M. Sc. **88**:31, 1884.

9. Roth, M.: Virchows Arch. f. path. Anat. **86**: 372, 1881.

10. Poncher, H., and Miller, G.: Am. J. Dis. Child. **45**:1064, 1933.

11. Edwards, H.: Brit. J. Surg. **17**:7, 1929.

12. Kimpton, A. R., and Crane, D. R.: Am. J. Surg. **49**:342, 1940.

a duplicate on the mesenteric border. In all 3 specimens the free portion is provided with a bulbous blind end which may project freely into the peritoneal cavity or be buried subperitoneally in the body wall. The specimens shown in *3* and *4* (fig. 4) already begin to show this characteristic. The bulb is always at the opposite end from the mouth of the duplicate, whether this opening is oral or aboral.

The third type of duplication, much rarer than those already described, can be explained only as the result of a condition such as is shown in figure 3, *f* and *g*. The duplicate opens into the parent tube at both ends, but in its central portion it is entirely free, with a mesentery of its own. The intestinal tract thus appears split in two lengthwise for a certain distance, each half resembling a perfect intestine with all its layers

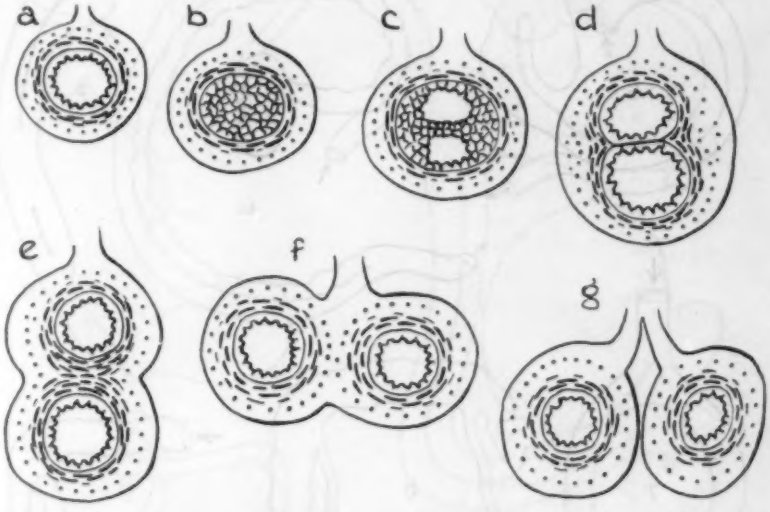

Fig. 3.—Diagram of the development of duplication: (*a*) early stage; (*b*) solid stage; (*c*) two vacuoles in the cell mass; (*d*) two epithelial lumens, with conjoined basement membranes; (*e*) conjoined circular muscle layer between the lumens; (*f*) the same in horizontal position, leading to (*g*) free duplicate tubes, each with a complete intestinal wall and a separate mesentery.

complete. The first example (fig. 4*7*) is represented in the obviously stylized drawing by Blasius[13] (1711), which is the earliest record I have found of any type of intestinal duplication. It represents an esophagus doubled for the extent of five or six vertebrae, found in a child of 5 years. Blasius said that he had previously seen a similar anomaly in a newborn infant. The second case of this loop form of duplicate (fig. 4*8*) is taken from Lockwood's[14] account of a condition found in a man of 57 years. The cecum is in the upper right quadrant, and the descending colon is divided, both tubes leading to a tumor mass in the sigmoid, in which they are lost. Lockwood warned that, because of the tumor mass, a lower meeting of the two parts of the colon cannot be proved. The third case (fig. 4*9*) is drawn from the description given in a personal letter by Robertson appended to the paper by Hudson.[15] The patient was a girl of 12 years. The large intestine was double. The lateral portion passed normally to the anus; the mesial tube opened by a pinpoint opening into the vagina. At first sight this does not seem to resemble the loop form, yet if one remembers that in the young embryo at the time when the chains of vacuoles, through which the duplication arose, are present the rectum and the vagina are still fused in the cloaca, the case becomes clearer. The loop ended in the cloaca, and as this was later subdivided one loop member remained with the dorsal or anal portion, the other with the ventral or vaginal portion, as occurs in cases of rectovaginal fistula. The original loop was made to appear open at the lower end by the later division of the cloaca. The final condition is the result of two unrelated anomalies.

Another case, similar to the last mentioned in representing the combination of two unrelated anomalies, has recently been reported by Ladd and Chisholm.[16] One limb of a duplicate of the rectum opened normally at the anus, while the other limb connected with another opening, more ventrally placed. The anterior opening was thought to be the vagina, giving the picture of

13. Blasius, G.: Observationes medicae anatome rariores, Amstelodami, Langerach, 1711.

14. Lockwood, C. B.: Brit. M. J. **2**:574, 1882.

15. Hudson, H.: New England J. Med. **213**:125, 1935.

16. Ladd, W. E., and Chisholm, T. C.: Am. J. Dis. Child. **66**:629, 1943.

rectovaginal fistula, as in the last case. On more thorough examination, however, two laterally placed vaginal openings were discovered, connected with two uteri and tubes. The anterior anal opening must therefore be due to the continuation of the duplication through the cloaca in its solid stage. The double uterus was an unrelated anomaly.

A group of cases closely similar to the case just described shows the long loop formation and Meckel, respectively). In the first example a duplicate is present extending from the first part of the duodenum to and including the cecum and the appendix. The splitting of the cecum and the appendix is more readily understood if one realizes that at the time of duplication these two organs are represented by a small spindle-shaped enlargement in the course of the hindgut. One cecum is continued by a minute straight undeveloped large intestine leading to the anus;

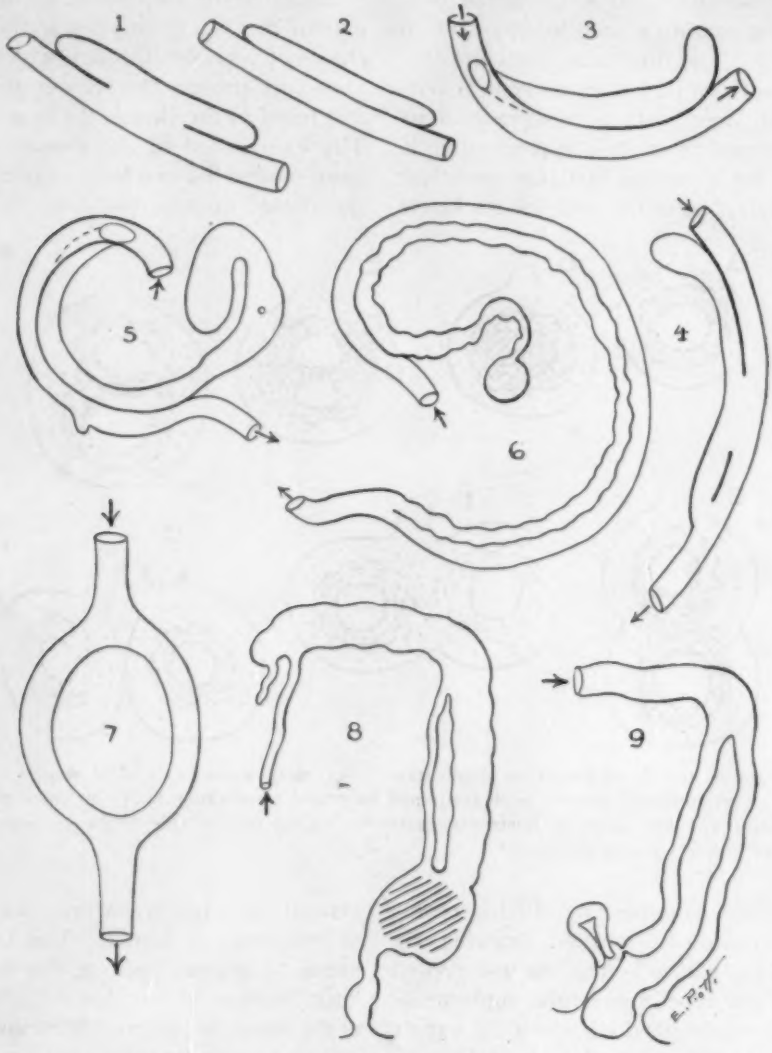

Fig. 4.—*1* to *6*, various more common types of intestinal diverticula, closed, open at center, open at oral or aboral ends; *7*, loop duplication of the esophagus, obviously stylized; *8* and *9*, loop duplications of the colon and the sigmoid flexure, one limb of *9* opening into the vagina. In *5* the small circle indicates a gastric ulcer. The diagrams represent cases described in the literature and are fully described in the text.

with the added complication of atresia of some portion of the intestinal tract. Three examples of this condition have been recorded (fig. 5 *1*, *2* and *4*, from Fairland,[17] Feingold and Shulman [18]

the other cecum ends blindly. This formation cannot be the result of the development of a diverticulum however much it resembles that, for two reasons: (1) the development of a cecum and an appendix at the end of a diverticulum of the duodenum is as nearly impossible as anything in embryologic growth can be and (2) the

17. Fairland, F.: Brit. M. J. **1**:851, 1879.

18. Feingold, B. F., and Shulman, A. G.: Am. J. Dis. Child. **63**:541, 1942.

tube in question could not have reached such a length without the blood supply from a mesentery, which is absent in the case of diverticula but a necessary result in the formation of free duplicates. The condition probably arose following atresia of the colon immediately beyond one cecum, a theory made much more probable by

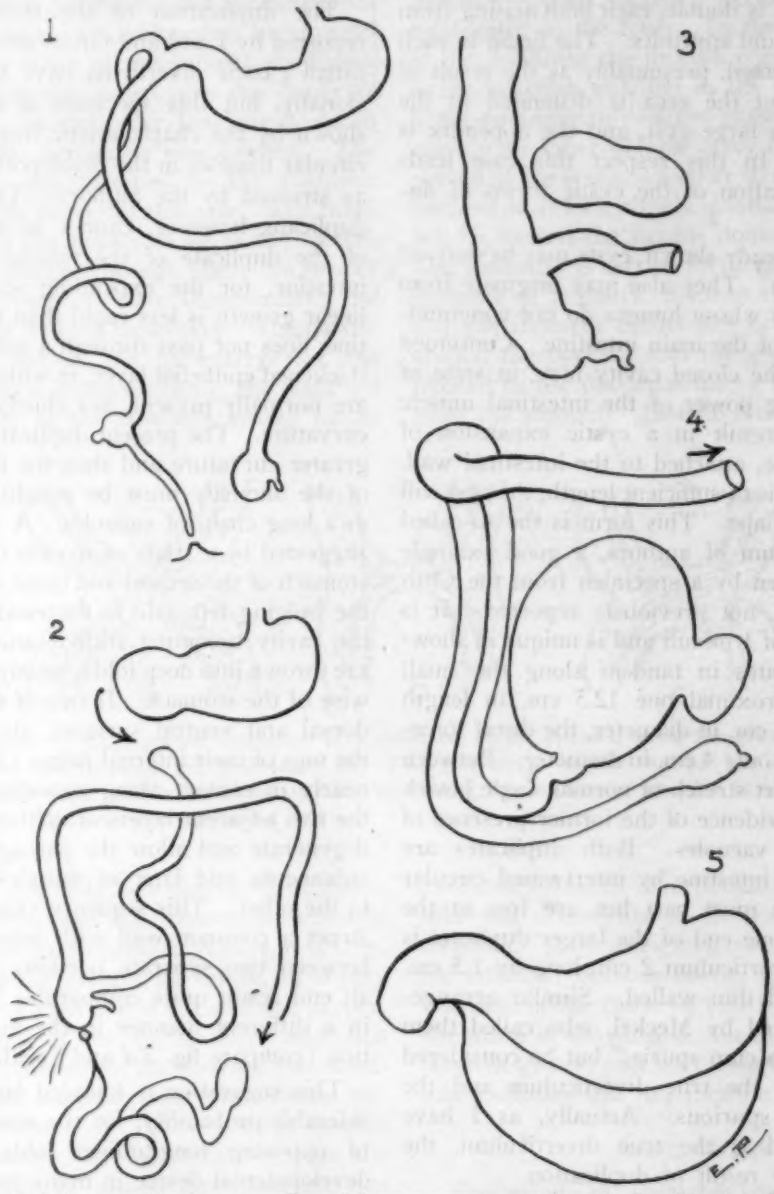

Fig. 5.—*1, 2* and *4,* loop duplications complicated by concurrent atresias. *3,* closed cyst derived by duplication; *5,* duplication of stomach. The diagrams represent cases described in the literature. Full descriptions of the anomalies are given in the text.

extreme underdevelopment of the remaining colon.

In the case described by Feingold and Shulman (fig. 5 *2*), in some respects very similar to the last, the long loop of the duplicate probably originally extended from the duodenum to and including the cecum. Here also one member became detached by atresia, but in this case the cecum and the proximal part of the ileum suffered stenosis above the actual atresia and remained underdeveloped. The tiny bulb terminating this tube lies in the same bit of mesentery as the more normal cecum, a fact which makes more certain the interpretation of the former as a minute twin cecum. This specimen differs, moreover, from the last in the presence of a second area of atresia, which included at least the upper fork of the loop, perhaps much more. The stomach ends blindly, and the two members of the supposed loop begin blindly. The position of one of the ends near the pylorus indicates that

in this member the atresia was local, but the fact that the other member was located entirely in the right lower quadrant, as described by the authors, suggests that extensive atresia destroyed all but the lower part of the ileum.

A variant of this same type is shown in another case drawn by Meckel (fig. 5 *4*). Here the ascending colon is double, each limb arising from its own cecum and appendix. The ileum in each case is unconnected, presumably as the result of atresia. One of the ceca is distended to the dimensions of a large cyst, and the appendix is also swollen. In this respect this case leads to the consideration of the cystic forms of duplication.

As I have already shown, cysts may be derived from diverticula. They also may originate from short duplicates whose lumens do not communicate with that of the main intestine. Continued secretion into the closed cavity may, in spite of the constraining power of the intestinal muscle layers, finally result in a cystic expansion of considerable size, attached to the intestinal wall. If the duplicate is of sufficient length, the cyst will be tubular in shape. This form is the so-called giant diverticulum of authors, a good example of which is given by a specimen from the Children's Hospital, not previously reported. It is from an infant of 1 month and is unique in showing two duplicates in tandem along the small intestine, the proximal one 12.5 cm. in length and from 3 to 7 cm. in diameter, the distal somewhat longer but only 4 cm. in diameter. Between the two is a short stretch of normal single bowel. Here one has evidence of the former presence of two chains of vacuoles. Both duplicates are attached to the intestine by intertwined circular muscles for the most part but are free at the two ends. At one end of the larger duplicate is a small true diverticulum 2 cm. long by 1.5 cm. in diameter and thin walled. Similar arrangements were noted by Meckel, who called them diverticula "vera cum spuria," but he considered the larger part the true diverticulum and the outgrowth the spurious. Actually, as I have shown, the bud is the true diverticulum, the parent stem the result of duplication.

In this case the normal bowel was open and somewhat enlarged from some unknown cause, perhaps one similar to that which produces megacolon. In 2 cases of intestinal cyst due to closure of a duplicate described by Ladd and Gross (their cases 8 and 17) the cyst had grown to such a size and tension as to flatten the accompanying bowel to the point of occlusion.

The duplication cyst may become entirely separate from the main intestine and lie free in the abdominal cavity except for being attached by its own mesentery (fig. 3 *g*). Such is the cyst described by Millar and Robertson [19] (fig. 5 *4*), whose origin is proclaimed by its elongated shape and by the fact that it showed the full number of intestinal layers, which, as has been noted, is impossible in a cyst of diverticular origin.

The duplication of the stomach (fig. 5 *5*) reported by Ladd and Gross seems to be unique. Small gastric diverticula have been noted occasionally, but this specimen is a duplication as shown by the characteristic interweaving of the circular muscles in the fused portion of the walls, as stressed by the authors. The origin of the duplicate, however, cannot be exactly like that of the duplicate of the tubular portion of the intestine, for the expanding stomach, since its linear growth is less rapid than that of the intestine, does not pass through a solid stage and the thickened epithelial layer, in which a few vacuoles are normally present, lies chiefly near the lesser curvature. The present duplicate runs along the greater curvature and thus the underlying cause of the anomaly must be sought elsewhere than in a long chain of vacuoles. A possible cause is suggested by a study of models of the embryonic stomach of the second and third month. In these the bulging left side is flattened dorsoventrally, the cavity becoming slitlike, and here the walls are thrown into deep folds, mostly running lengthwise of the stomach. If two of these folds, from dorsal and ventral surfaces, should meet along the tops of their internal ridges (I have seen them nearly in contact along considerable distances), the two adjacent layers of epithelium might fuse, degenerate and allow the passage of a bridge of submucosa and later of muscles from one wall to the other. This sequence (fig. 6) would construct a common wall with intertwined muscles between two separate portions of the stomach, an end result quite comparable to that achieved in a different manner in the intestinal duplication (compare fig. 3 *d* and *f* with fig. 6 *b* and *c*).

This suggestion is founded on a basis of considerable probability, for the meeting and fusing of opposing longitudinal folds is a common developmental device in many parts of the body. The principle is involved in the normal division of the foregut into the trachea and the esophagus, of the primarily single aortic trunk into the definitive aorta and the pulmonary trunk and of the common cloaca into the urethra and the rectum, to mention a few instances. In all such cases there must be at one period of the separation a fused common wall as in this stomach.

19. Millar, R. E., and Robertson, G.: Brit. J. Surg. **17**:372, 1930.

In the absence of any other probable cause for the present anomaly this suggestion may well stand as the correct explanation and the specimen be recognized as a duplication of unusual origin.

In a few only of these reports of cases is specific mention made of peristalsis in the duplicate portion. In the isolated cyst studied by Millar and Robertson [19] active peristalsis and antiperistalsis could be elicited for two hours after its surgical removal, and in some of the tubular duplicates similar activity is also noted. In the duplicate of the stomach, on the other hand, it is stated definitely that no peristalsis was evident. The differences may be explained by the anatomic distribution of the nerves in this case. The tubular duplicates of the intestines lie in the mesenteries and can receive through them the proper vessels and nerves for their musculature; the isolated cyst had its own mesentery. The gastric duplicate also lies in the mesentery—for the greater omentum is embryologically the distorted dorsal mesentery of the stomach, swung far to the left side of the body and greatly distended—but this mesentery does not transmit both vessels and nerves. The gastroepiploic vessels, it is true, run in it along the greater curvature, to supply the duplicate and a portion of the stomach proper, but the branches of the vagus nerve approach from the lesser curvature, not through the omentum. One may suppose that their motor terminals, now located in the myenteric plexus between the muscle layers, could not pass the barrier of interlaced musculature between the main stomach and the duplicate and that because of this block the muscles of the latter never assumed activity. The absence of peristalsis in the gastric duplicate is thus explicable on the basis of the normal distribution of the gastric nerves. Certainly peristalsis is to be expected in duplicates of the more common type.

The longer open tubular duplicate usually develops a swollen or rounded terminal bulb at the end opposite to the opening, whether this opening is oral or aboral. This shape is probably due to the continued impact of the fluid contents driven by peristaltic or antiperistaltic waves transmitted along the duplicate against the blind end. That the bulb is already present before birth does not vitiate this theory, for it has been amply demonstrated by Speert [20] that active peristalsis is well established in the fetus. In the tubular portion of the duplicate the mucosa corresponds to that in the adjacent gut, but in the bulb the mucosa is almost invariably of the gastric type, and frequently an inner oblique layer of muscles is reported in the walls. In other words, the bulb has become, or at least closely simulates, a small stomach or, better, the fundus dome of the stomach. The similarity is carried further by the occasional presence of a gastric ulcer in the sac (fig. 45) and the frequent occurrence of "gastric" ulcers around the opening into the gut, which may be likened to the duodenal ulcers found at the exit from the stomach. Gastric mucosa is also often found in Meckel's diverticulum and in the open spherical diverticula of the esophagus and the intestine. It is intriguing to speculate whether the enlarged bulbous shape, reminiscent of the stomach, is the cause of this type of heterotopic alteration in the mucosa, but the irregular occurrence of gastric patches throughout the intestinal tube indicates that the question is more complex.

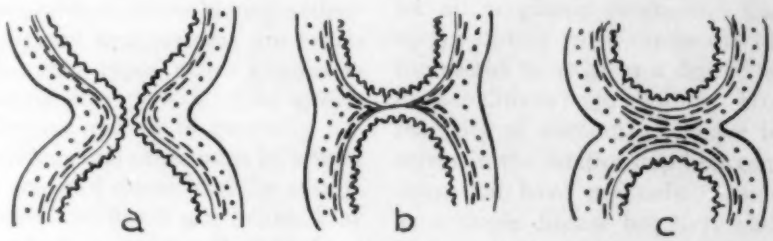

Fig. 6.—Diagram of the supposed derivation of a duplicate of the stomach along the greater curvature: (*a*) Two folds of the gastric wall are touching. (*b*) The epithelium wherein contact has disappeared and the opposite layers have fused with a common basement membrane. (*c*) Circular muscles have grown between as interwoven fibers. Compare with figure 3 *d* and *e*.

CONCLUSIONS

The group of anomalies comprising the enterogenous cysts, intestinal duplications and the like is divisible into two smaller classes on the basis of embryologic origin. Most of the spherical cysts are derived from true diverticula, which are frequently found projecting from the ventral or antimesenteric surface of the tube in embryos of the eighth or ninth week and are normally absorbed later. Abnormally they continue to

20. Speert, H.: Am. J. Obst. & Gynec. **45**:69, 1943.

grow: If restricted by the intestinal muscle, they bulge within the lumen, but if they pierce the muscle layers, outward expansion is not limited and they may become large cysts attached to the intestine. Their wall is necessarily thinner than the gut wall.

A few of the spherical and most of the tubular structures represent true duplication, originating by an abnormal persistence of the vacuoles normally present among the massed cells of the "solid stage" of the intestine, a phenomenon of growth in embryos of the sixth or seventh week. By the confluence of a chain of vacuoles a new channel is formed, parallel to the original lumen, and becomes separated from the latter by a union of the intestinal layers between the two. Since the duplication develops within the intestine, the outer wall of the duplicate portion always contains all of the tissue layers of the intestine. The duplicate lumen usually lies between the leaves of the mesentery but may be entirely separated, with a mesentery derived by the splitting of the original. It may open into the main lumen at one or more places, or become a closed cyst. Theoretically, three or more channels are possible, the main lumen and two or more confluent chains of vacuoles.

The duplicate structures assume many forms, some of which are shown and described, and are often associated with other anomalies. In the tubular portions the mucosa tends to resemble that of the parent tube, but in bulbous or cystic portions it changes to the gastric type. Great internal pressure may destroy mucosa of any type.

CARCINOMA IN YOUNG PERSONS

ROBERT P. MOREHEAD, M.D.

WINSTON-SALEM, N. C.

The malignant tumors constitute a group of diseases which possess certain fundamental characteristics in common but which differ from one another in details of such consequence as to necessitate their separate consideration as well defined entities. Thus the many types of malignant neoplasms fall into clearcut groups differing as to the time of appearance, as to the histologic picture and apparently also as to the causative agent.

Neoplasia is essentially a disturbance in growth resulting in lesions of various types which appear characteristically at well defined times in life. During infancy and early childhood certain types appear which are extremely rare in the latter years of life. Adenosarcoma of the kidney, retinoblastoma and malignant neurocytoma are excellent examples of tumor types which characteristically arise during this period. Histogenetically, their embryonic nature is generally admitted, and the fundamental cause must be sought in some inherent defect of the cells of the anlage.

Infancy and early childhood are followed by a phase of life which is practically free from neoplastic growth. This may be designated as late childhood or as the presexual period. Ewing [1] pointed out that the decline in the incidence of malignant tumors during this period is a point of fundamental biologic importance, for it suggests that the causative factors of the tumors of infancy have exhausted themselves and that for tumors occurring thereafter new etiologic factors must be sought.

The period of life following the presexual period has been designated by Pack and Le Fevre [2] as puberty. It is interesting to note that during this period only one important group of tumors reach their greatest incidence. These, of course, are the various types of sarcoma of bone. This fact is not without etiologic significance, for this is one of the most critical stages in the process of osteogenesis. It is conceivable that primitive connective tissue rests may be stimulated to neoplasia by growth-initiating factors similar to those which bring about the orderly development of bone.

Regarding incidence, the majority of malignant tumor groups reach their peak after the age of 40. This is especially true of the carcinomas. Even here, however, one must consider each type of carcinoma as a separate disease entity and avoid dangerous and misleading generalizations. These will inevitably follow if an attempt is made to find a common denominator for all neoplastic processes. Carcinoma of the cervix differs from carcinoma of the fundus of the uterus to as great a degree as one infectious disease differs from another. Unfortunately, the majority of authors who have interested themselves in the relationship between age and tumor formation have not only considered carcinoma as a single disease but have had a tendency to include all neoplastic processes in the same category. Their results have therefore necessarily been inconclusive, and they have failed to establish any clearcut facts as to the influence of age on the behavior of malignant tumors. As a result of this attitude of mind, carcinoma in the young has been robbed of its rightful place in the study of neoplastic processes, and the characteristics which are peculiar to it have been lost in the confusion of generalizations.

It is the purpose of this paper to report a group of cases in which types of tumor expected in adult life have occurred precociously. Especial attention is given here to their incidence, morphologic character and course. An attempt will be made to compare this group with other groups of neoplasms which occur at a more orthodox time in life. Limits of space make it impossible to cover adequately the entire field of the types of carcinoma occurring in young persons and the report will therefore be confined to certain of the more important types of gynecologic interest, with a brief consideration of primary cancer of the liver. Certain other types will be considered in a subsequent report.

From the Department of Pathology, Bowman Gray School of Medicine, Wake Forest College.

Read before the Section on Pathology and Physiology at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, June 15, 1944.

1. Ewing, J.: A Survey of Cancer in Childhood, in Dargeon, H. W.: Cancer in Childhood, St. Louis, C. V. Mosby Company, 1940.

2. Pack, G. T., and Le Fevre, R. G.: J. Cancer Research **14**:167, 1930.

TABLE 1.—*Distribution of Types of Cancer According to Periods*

Infancy and early childhood	Adenosarcoma of (kidney) Retinoblastoma Malignant neurocytoma of gland (adrenal)
Late childhood or presexual period	Fewer tumors appear than at any other period of life
Puberty	Sarcoma of bone Tumors of adult life begin to appear and those of childhood to disappear
Young Adult	Precocious cases of adult tumors increase in number
Middle Life	Malignant lymphoma Carcinoma of cervix Carcinoma of breast
Old age	Carcinoma corpus uteri Carcinoma of liver Carcinoma of stomach Carcinoma of rectum

CARCINOMA OF THE CERVIX

Carcinoma of the cervix is a disease of the reproductive period of life and reaches its greatest incidence during the fifth decade. It is of common occurrence in the fourth decade and is not rare between the ages of 20 and 30. Of 254 specimens of cervical carcinoma sent to our laboratory over a period of ten years, 20 were obtained from patients in the third decade of life.

Carcinoma of the cervix occurring at or below the age of 20 years is an extremely rare condition. Bowing and McCullough [3] reviewed the literature in 1941 and could find only 11 cases of carcinoma of the cervix falling into this age group. To these they added a case of their own. They overlooked the case reported by Scheffey and Crawford,[4] in which carcinoma of the cervix occurred in a 22 month old child. Since the article by Bowing and McCullough appeared, additional cases have been reported by Glass [5] and by Shaw,[6] bringing the total to 15. To these I wish to add 2 more cases. One of the patients was a girl 19 years of age and the other a girl of 20.

CASE 1.—A. S., a 20 year old student nurse, was admitted to the H. F. Long Hospital, Statesville, N. C., Jan. 19, 1942, complaining of menorrhagia. Menstruation had begun at the age of 12, and the periods had occurred regularly every twenty-eight days, lasting five days. Five months prior to admission she began to menstruate at the regular time and continued to bleed until the time of admission. Pelvic examination revealed no abnormal masses, and the uterus was found to be normal in size and position. An irregular, friable growth covered the greater part of the vaginal surface of the cervix, and bleeding from this organ was profuse. A biopsy revealed squamous cell carcinoma, grade 2. Radium therapy was instituted. Examination on May 13, 1944 revealed no evidence of a recurrence of the disease. The patient is now doing general nursing duty and presents no symptoms referable to carcinoma.

TABLE 2.—*Carcinoma of the Cervix in Patients Twenty Years of Age or Under*

Case	Author	Year	Age of Patient	Morphologic Type	Result
1	Boyd	1906	18	Adenocarcinoma	Well 1 year
2	Glöckner	1908	7	Adenocarcinoma	Well 3 years, metastasis in 4th year
3	Wells	1913	18	Adenocarcinoma	Well 4 years
4	Darnell	1920	20	Adenocarcinoma	Died of pulmonary embolism postoperatively
5	Lisa and Cornwall	1926	16	Squamous cell carcinoma	Dead, 5 months
6	Bonner	1927	13	Adenocarcinoma	Well, 19 months
7	MacDonald	1929	10	Adenocarcinoma	No follow-up
8	Morse	1930	10	Adenocarcinoma	Dead 1 year
9	Ludwig	1936	16	Adenocarcinoma	Alive 5 years
10	Bowing and McCullough	1941	13	Adenocarcinoma	Well 6 years
11	Tschop	1897	19	Not given	Not given
12	Cragin	1913	18	Not given	Well 4 months
13	Scheffey and Crawford	1932	22 mo.	Adenocarcinoma	Dead 7 weeks
14	Glass	1933	16	Adenocarcinoma and squamous cell carcinoma	Dead 3 years, 3 months
15	Shaw	1941	15	Adenocarcinoma	Dead 8 months
16	Morehead	1944	19	Squamous cell carcinoma	Dead 3 months ?
17	Morehead	1944	20	Squamous cell carcinoma	Well 2 years, 4 months

CASE 2.—A Negro girl aged 19 was admitted to the Goldsboro Hospital, Goldsboro, N. C., complaining of a vaginal discharge of "several months'" duration. The patient believed herself to be pregnant. A record of the past history could not be obtained. On examination, the fundus of the uterus was found to be enlarged to the size of a five months' pregnancy, and fetal heart sounds were heard. There was a profuse, foul, grayish white vaginal discharge and a large fungating cauliflower-like mass was noted on the anterior lip of the cervix, extending into the vaginal vault. Conization of the cervix was performed. The vagina was packed, and two days later the patient delivered a 5 month old fetus. Microscopic examination of the cervical tissue revealed squamous cell carcinoma, grade 2. Repeated efforts failed to locate the patient after her discharge from the hospital.

Cervical carcinoma is a disease occurring in all decades of life, but, as was stated previously,

3. Bowing, H. H., and McCullough, J. A. L.: Am. J. Roentgenol. **45**:819, 1941.

4. Scheffy, L. C., and Crawford, B. L.: Am. J. Obst. & Gynec. **24**:118, 1932.

5. Glass, M.: Am. J. Obst. & Gynec. **26**:104, 1933.

6. Shaw, W. F.: J. Obst. & Gynaec., Brit. Emp. **48**:239, 1941.

the incidence reaches its peak in the fifth decade. Most authors are of the opinion that those cases in which this type of cancer occurs in the third and fourth decades offer a much poorer prognosis than those in which it appears at a later date. Scheffey,[7] after a careful study of 293 cases of cervical carcinoma, concluded that "the percentage of surviving patients who were over 40 years of age when they received their initial treatment is about twice as large as the corresponding percentage of survivors under 40." In other words, the older patients have done twice as well as regards survival as have the younger ones.

From a study of the available cases of cervical carcinoma occurring in the first two decades it is apparent that age exerts a definite influence on the morphologic type of carcinomas encountered. In general, adenocarcinoma constitutes only about 5 per cent of the epithelial cancers which arise in the cervix, yet of the 15 reported cervical cancers proved to be carcinoma in persons 20 years of age or under, more than two thirds were adenocarcinoma.

It will be noted further from this small group that squamous cell carcinoma is rapidly fatal in the young, while adenocarcinoma offers a much better prognosis. This situation is somewhat different from the usual one, for, as Martzloff [8] pointed out, adenocarcinoma of the cervix occupies a position between the spinal cell and transitional cell types of epidermoid carcinoma as far as relative malignancy is concerned. Warren [9] studied the distribution of metastases of all types of cervical carcinoma and concluded that adenocarcinoma was approximately of the same degree of malignancy as epidermoid carcinoma of grade 2. Youth, then, is not only a factor in determining the type of tumor encountered but also greatly alters the prognosis for that particular type.

CARCINOMA OF THE BODY AND FUNDUS OF THE UTERUS

Carcinoma of the body and fundus of the uterus is a disease which most frequently arises in the sixth decade of life, the average age of its appearance being approximately 58 years. In contrast to carcinoma of the cervix, which is fairly frequent between the ages of 20 and 30, carcinoma of the fundus of the uterus is extremely rare in the third decade of life. Of 732 patients with pure carcinoma of the body of the uterus seen at the Mayo Clinic over a period of twenty-three years, only 1 was under 30 and she was aged 29.[8] Scattered reports of cases of carcinoma of the fundus occurring in a young person are to be found in the literature,[10] but they are too few to allow one to arrive at definite conclusions regarding the influence of age on the morphologic character and course. Of 104 specimens of carcinoma of the body of the uterus sent to our laboratory over a ten year period, 3 were from patients under the age of 30. This is an unusually high number and is out of proportion to the numbers recorded for other series of cases which have been reported.

CASE 1.—L. A., a white woman aged 25 years, single, consulted her physician Sept. 27, 1940, with the chief complaint of dysmenorrhea. Menstruation had begun at the age of 13 and had occurred every twenty-eight days, lasting from six to seven days. Dysmenorrhea had always been severe, but for several months previously the pain had been less severe. At her last period there was a profuse flow, and this, together with the rather marked dysmenorrhea, caused her to consult her physician. On examination the uterus was found to be in good position. A mild erosion was noted on the cervix, and a small amount of mucopurulent discharge could be seen. With the patient under ether anesthesia, the cervix was dilated and the uterus curetted, but only one piece of tissue, measuring approximately 1 cm. in diameter, was obtained. Microscopic examination revealed grade 1 adenocarcinoma originating in the base of an endometrial polyp. This diagnosis was confirmed by Dr. Wiley Forbus, of Duke University. Panhysterectomy and unilateral salpingo-oophorectomy were then performed. Examination in May 1944 revealed no evidence of recurrence of the tumor.

CASE 2.—S. D., a white woman 29 years of age, a widow, consulted her physician June 1, 1942, complaining of pain in the upper part of the abdomen of six months' duration. She had been perfectly well prior to the onset of this illness. Menstruation had begun at the age of 13 and had always been markedly irregular. Her periods had lasted from four to five days and had come at intervals of fifteen to forty-five days. At the onset of her present illness this irregularity became more marked. The patient had married at the age of 20 and lived with her husband until he was killed in an accident two years previously. There had been no pregnancies, although no contraceptives were used. On examination, the edge of the liver was felt about 1 inch (2.5 cm.) below the costal margin, and a firm mass was palpated in the epigastrium. Vaginal examination revealed a small amount of bleeding. The cervix appeared to be perfectly normal. The fundus of the uterus was not felt, but the cervix appeared to be fixed to a mass posteriorly. On rectal examination this mass was palpated about 2 inches (5 cm.) from the anal orifice. It had narrowed the lumen of the bowel to such a degree that the examining finger could not be passed through. The clinical diagnosis was inoperable carcinoma of the rectum with metastasis to the liver. The patient went rapidly downhill and died on the third hospital day. At autopsy it was found that the endo-

7. Scheffey, L. C.; Thudiam, W. J., and Farell, D. M.: Am. J. Obst. & Gynec. **43**:941, 1942.

8. Martzloff, K. H.: Bull. Johns Hopkins Hosp. **34**:141 and 184, 1923.

9. Warren, S.: Arch. Path. **12**:783, 1931.

10. Lockhart, H. A.: Am. J. Obst. & Gynec. **30**: 76, 1935.

metrium had been replaced by an anaplastic type of carcinoma which had extensively invaded the wall of the organ and the parametrium and had extended inferiorly to produce the mass which was felt on rectal examination. Metastatic lesions were found in the regional lymph nodes, the liver and the lungs.

CASE 3.—A. P., a white woman aged 27, married, consulted her physician Jan. 11, 1939 because of abnormal vaginal bleeding of six weeks' duration. Menstruation had begun at the age of 12 and had been irregular all of her life, coming at intervals of four weeks to three months and lasting three to seven days. During the year previous to admission she had menstruated every two weeks, and for the last three months there had been almost constant bleeding. She had married at the age of 16, but there had been no pregnancies.

On examination she was found to be obese, weighing approximately 200 pounds (90.5 Kg.). The fundus of the uterus was normal in size and position, and no masses were palpable. Bleeding from the cervical canal was noted, but otherwise the examination gave negative results. A diagnostic dilation and curettage were performed, and a diagnosis of adenocarcinoma of the body of the uterus, grade 2, was made. The uterus was removed by the vaginal route, and both ovaries were normal to palpation at that time. The patient has had no recurrence of the carcinoma, but it is interesting to note that in 1942 she had a coronary occlusion.

There is a fairly definite relation between the decline of functional activity of the endometrium and the development of cancer. The cases in which cancer has occurred in youth are so few that definite conclusions regarding the influence of age on the morphologic character and course cannot be drawn from them.

Morphologically, it is interesting to note that fundal carcinoma of young women does not differ in microscopic appearance from that of older women. My 3 specimens of precocious uterine carcinoma differed from one another as to morphologic type but were similar microscopically to the uterine carcinoma ordinarily encountered in the later decades.

It is evident from a review of the literature that most authors believe that there is no correlation between the microscopic grade of malignancy in cervical carcinoma and the ultimate course of the disease. On the other hand, there is more or less unanimity of opinion that in carcinoma of the uterine body there is a distinct relation between the microscopic grade of malignancy and the life expectancy of the patient. Although the 3 cases reported here are not statistically significant, they give support to this idea; for in those in which the malignancy was of low grade there have been no further symptoms for more than five and three years, respectively, whereas in the case in which it was of grade 4 the disease ran a rapid and fulminating course, having a duration of only six months after the appearance of the first symptom. The grade of malignancy seems to be the all-important factor in this disease. The next step should be toward the determination of the influence of age on the grade and the morphologic type of the tumor, for it appears that once the microscopic picture has been established, the prognosis has been settled.

PRIMARY CARCINOMA OF THE LIVER

Primary carcinoma of the liver characteristically occurs between the ages of 40 and 60 but is seen at all periods of life. The disease has been seen in newborn infants, and Steiner [11] has collected 75 cases in which it arose during childhood. In 41 of these cases, or 53.2 per cent, it occurred before the age of 2 years. I have observed primary carcinoma of the liver in 2 young patients, aged 13 and 18.

CASE 1.—F. H., a white boy aged 13, was first seen by his physician on Oct. 6, 1937, when he complained of pain in the upper right side of the abdomen and of nausea and vomiting of two days' duration. His father stated that the boy had not felt well for the preceding three months and that during this time he had had occasional bouts of nausea and vomiting. Examination revealed a chronically ill patient with severe jaundice and a temperature of 100 F. The liver could be palpated down to the umbilicus. The urine showed a reaction for albumin (2 plus) and a strongly positive reaction for bile; it contained 40 leukocytes per low power field. There were 1,950,000 red blood cells per cubic millimeter, and the icterus index was 136. On November 1 the patient was operated on. The liver was observed to be greatly enlarged but smooth, and the peritoneal cavity was filled with blood. The patient went rapidly downhill and died November 13, slightly more than four months after his initial symptoms. At autopsy the liver was found to be tremendously enlarged; a firm tumor had replaced the greater portion of the right lobe and had involved secondarily the regional lymph nodes, the gallbladder, the cystic duct, the pancreas and the left lung. Microscopically, all tumor tissue was characteristic of liver cell carcinoma.

CASE 2.—A white youth aged 18 first consulted his physician Jan. 22, 1936 because of swelling in the upper part of the abdomen. He stated that his abdomen had been swollen for several weeks and that three weeks prior to admission he had an attack of "pleurisy." Examination revealed a greatly enlarged liver, extending below the level of the umbilicus, definite icterus, marked anemia and moderate leukocytosis. At operation the liver was found to be enormously enlarged and nodular. The peritoneal cavity contained a large collection of fresh blood and some clots. After a biopsy specimen had been taken from the liver and a large amount of blood removed from the peritoneal cavity, the abdomen was closed. The patient was given repeated transfusions, but he went rapidly downhill and died February 19, less than three months after his initial symptom of abdominal swelling. A diagnosis of primary carcinoma of the liver, bile duct type, was

11. Steiner, M. M.: Am. J. Dis. Child. **55**:807, 1938.

made from the biopsy specimen and was confirmed by Dr. Fred Stewart, of the Memorial Hospital for the Study of Cancer and Allied Diseases, in New York.

The occurrence of primary carcinoma of the liver in persons below the age of 40 is not extremely rare. Its occurrence in newborn infants and in very young children suggests that at least in some cases congenital factors may play a part in the etiology. There is apparently no relation between age and the course of the disease, since practically all patients with primary carcinoma of the liver are dead within four months after the appearance of the first symptom. Those cases in which the disease has occurred in a young patient offer no exception.

SUMMARY AND CONCLUSIONS

Age is one of the most important factors to be considered in any approach to the problem of neoplastic growth. Thus physicians see in infants and children characteristic types of tumor which in all probability are the result of inherent defects arising during the developmental process. The great majority of tumors of these types appear at an early period in life, but occasionally the cells which carry the intrinsic defect remain dormant for many years before they are stimulated to neoplastic growth. Primary carcinoma of the liver probably belongs to this group of neoplasms; for it has been pointed out that, although the disease occurs in all periods of life, it is not extremely rare in young children and has been described in newborn infants. However, recent experimental work indicates that additional factors may be operative in some cases. The disease is rapidly fatal, and age does not seem to influence its course or morphologic character. To those tumors diagnosed as primary carcinoma of the liver which have been reported as occurring in young persons, we have added 2 more, one in a boy of 13 and the other in a youth of 18.

After the embryonal factors have spent themselves, it is probable that two great factors operate in the production of cancers:[12] (1) intrinsic factors, both hereditary and environmental and (2) carcinogenic stimuli from the external environment. From an etiologic point of view, malignant tumors should never be considered collectively but always individually, an attempt being made to locate the fundamental defect leading to the development of a given neoplasm. Carcinoma of the cervix offers a good example of this concept, for it is probable that the high incidence of this type of tumor during the reproductive period of life is influenced by the activity of the ovarian hormones. It is the opinion of most authors that precocious carcinoma of the cervix runs a more rapid course than that occurring in the older age group. The most striking finding in this study is the influence of age on the morphologic type of carcinoma of the cervix. All types of malignant epithelial growths are rare in the cervix before the age of 20, but when such growths occur the great majority of them are adenocarcinoma rather than squamous cell carcinoma, which is found ordinarily in older patients. Two cases of carcinoma of the cervix occurring at or under the age of 20 years have been added to the 15 reported in the literature to date.

The influence of age on the development of the malignant epithelial neoplasms is well exemplified by carcinoma of the body of the uterus. This is a disease associated with the functional decline of the endometrium, and its precocious occurrence is extremely rare. The tumors of this type occurring in young persons which have been available for study have not differed morphologically from those seen in older women.

The course of fundal neoplasms occurring in young persons appears to be influenced for the most part by the morphologic type encountered. It has been impossible to determine the influence of age on the morphologic type of these tumors, for the cases reported in the literature are too few to be statistically significant. Three cases of carcinoma of the body of the uterus arising under the age of 30 have been added to those already reported.

12. Little, C. C.: The Influence of Intrinsic Factors on the Development of Tumors in Mice, in A Symposium on Cancer, Madison, Wis., University of Wisconsin Press, 1938.

ABSTRACT OF DISCUSSION

CAPTAIN J. EDWARD BERK, Utica, N. Y.: We in the Army deal largely with young people, and all of us have been impressed with the frequency of malignant tumors in this group. In the past two and one-half years at the Tilton General Hospital and at the Rhoads General Hospital, where I am assigned, 4 patients under the age of 35 with carcinoma of the stomach and 5 under the age of 20 with carcinoma of the large bowel were observed in the gastrointestinal section alone. My associates in the other sections have been equally impressed with the frequency with which they have encountered malignant tumors of the skeletal system, the respiratory system, the nervous system and the genitourinary system. The urologists have seen many malignant testicular tumors.

A young soldier with carcimoma of the stomach presented himself with symptoms and signs of obstruction of the large bowel. He had complaints due to widespread metastases in the pelvis, and yet he did not have any symptoms referable to the upper part of the abdomen. A young officer was hospitalized not long ago because of hematemesis. He had a carcinoma of the transverse colon, the initial and apparently sole

manifestation of which was the massive hemorrhage resulting from extension of the cancer into the stomach.

Recently, a young soldier was seen because of pain in the upper region of the abdomen and the right costovertebral area. He was found to have a huge, swollen testis, of which he had been aware for eight years and about which he was little concerned. This condition proved to be due to a teratoma. The symptoms for which he sought aid were due to hydronephrosis secondary to obstructive compression of the ureter by metastatic tissue.

The great lesson to be learned from the clinical standpoint is that young persons are by no means exempt or immune to neoplastic disease, also that the classic picture of malignant disease of various organs as one is accustomed to think of it is not necessarily the characteristic one.

DR. F. L. RECTOR, Lansing, Mich.: I should like to discuss the question of cancer in youth from the educational standpoint.

In my connection with the state health department in Michigan, I have in the last three years talked to the students of nearly 400 different high schools, collectively about 85,000 students, on the subject of cancer control.

As a result, the last year 3 students, because of what they heard in these talks before their assemblies or their classes, visited their physicians and found that they had cancer of one type or another. Many other students were induced to go to their physicians because of black moles, sores and things like that, observed either in themselves or in their parents.

This occurrence of cancer in youth is a matter that no physician who is interested in the problem of cancer can afford to overlook. In the State of Michigan, in the five years from 1938 to 1942, inclusive, there were 546 deaths from cancer in persons under the age of 20. That is over 100 deaths a year. In that group physicians have more or less arbitrarily placed leukemia because all agree, I think, that leukemia is a form of cancer, but in the International List of Causes of Death it is given a separate classification for some reason. But, barring leukemia, about 60 per cent of those 546 deaths were reported definitely as deaths due to cancer.

None of the communicable diseases, measles, smallpox, scarlet fever, poliomyelitis, diphtheria, acute rheumatic fever, whooping cough, comes anywhere near causing the number of deaths in the state of Michigan each year that cancer does. Tuberculosis is the only disease that stands ahead of it.

The percentage of cures in the younger age groups is not nearly as favorable as in the older age groups. The cancers in young people are more rapidly fatal, but that does not mean that they should be ignored. Through a program of continued constructive educational work a great deal can be done to bring this knowledge of cancer in youth to the younger age groups and to those responsible for their welfare. By that means it will be possible in time to prevent the development of a great many cancers in these same young people after they have reached middle and older life.

DR. ROBERT P. MOREHEAD, Winston-Salem, N. C.: I used the term "carcinoma" in the sense of a malignant tumor of epithelial tissue. Physicians are familiar with the fact that certain types of sarcoma characteristically appear in young people.

My interest in the matter was first stimulated by the fact that in looking through the departmental cross index, I found that over 100 malignant epithelial neoplasms had occurred in persons 30 years of age or younger. In that group were many with carcinoma of the gastrointestinal tract. Malignant ovarian tumors were also numerous, but in many instances it was difficult or impossible to decide whether they originated from epithelial or from mesodermal tissue.

It is also interesting to note that a case is on file in the laboratory with which I am associated, of squamous cell carcinoma arising in the external auditory canal of a 4 year old boy. This diagnosis has been confirmed by many observers.

The problem of malignant epithelial tumors in young persons is a large one and when the term "cancer" is employed in its broad sense to include all malignant neoplasms, the problem of cancer really does become tremendous.

RECENT RESEARCH IN THE PATHOLOGY OF BURNS

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BALTIMORE

As Fender [1] stated in 1933, "The total pathological picture in the case of fatal burns is rich and varied." The pathologic changes in nonfatal thermal injuries also present a complicated picture, and the chief advances within the past few years have been concerned with adequate therapeutic recognition of certain of the pathologic relationships. Only by this means can the mortality from burns be reduced.

In the study of burns, as in that of most conditions, the alterations can be divided into local and general changes. Following thermal trauma there is often a direct connection between the former and the latter. In the present article not all pathologic changes due to burns will be discussed, but only certain of these that have particular interest at this time because of recent research. Practically all the items listed, however, will be considered from the therapeutic standpoint as well as from that of pathology.

LOCAL PATHOLOGIC CHANGES

Edema.—The edema following thermal injury is one of the most outstanding results of such trauma. In human beings the loss is both into the tissues and from the burned surface in the form of weeping. The amount of edema is considerable and was shown experimentally by Blalock [2] (1931) to be sufficient to cause shock in some instances (i. e., 3.34 per cent of the body weight). The nature of the fluid is of importance and was shown by Beard and Blalock [3a] (tissue edema fluid) and by McIver [3b] (blister fluid) and others to be essentially plasma-like. The rate of formation of the fluid is rapid, the outpouring occurring largely during the first eighteen hours and practically stopping after the first forty-eight hours.

With the rapid formation of large amounts of plasma-like fluid, the therapeutic implications would seem to be clear and are presented in part in table 1. The use of pressure dressings (Koch [4]), of plaster casts (Levenson and Lund [5]) or of cold as advised by Dr. F. M. Allen, of New York (Scientific Exhibit at the meeting of the American Medical Association in 1944), represents an external method of controlling loss of fluid, while the recent paper of Berman, Peterson and Butler [6] introduces an internal method of accomplishing the same thing. These authors injected isotonic solution of sodium chloride hypodermically into burned areas in anesthetized experimental animals. Such an injection increases the hydrostatic pressure within the tissues and apparently in this manner minimizes leakage of plasma. As a result of this treatment the survival time was considerably increased in animals so treated.

TABLE 1.—*Relation of Local Therapy of Burns to the Treatment of Shock Due to Burns*

Cause.—Shock attending a burn is in large part due to loss of plasma from the burned skin (weeping) and into the burned tissues (edema). It is aggravated by pain, toxemia and sepsis.
Time of Onset.—Shock begins at the time of the burn and is most severe during the first twenty-four hours; it usually abates by the forty-eighth hour.
Treatment.—Local therapy of the burn may help to prevent shock. There are two directives:
1. Decrease loss of plasma. Chemical escharotics (e. g., tannic acid) prevent weeping but do not stop loss into the deeper tissues. Since about 60 per cent or more of plasma loss is in the form of edema, chemical escharotics are of only partial value in stopping loss of plasma. Pressure dressings not only minimize weeping but also control much of the formation of edema.
2. Minimize pain and toxemia and prevent sepsis. Aseptic compression dressings are of especial value in this regard.

Evans and Hoover [7] pointed out that in burns of the second degree most of the loss of plasma is to the exterior in the form of weeping while in burns of the third degree it is chiefly into the tissues:

From the Department of Surgery, Johns Hopkins Hospital.

This paper was read before the Section on Pathology and Physiology of the American Medical Association in Chicago, June 16, 1944.

1. Fender, F. A.: Surg., Gynec. & Obst. **67**:612, 1933.

2. Blalock, A.: Arch. Surg. **22**:610, 1931.

3. (*a*) McIver, M. A.: Ann. Surg. **97**:670, 1933. (*b*) Beard, J. W., and Blalock, A.: Arch. Surg. **22**: 617, 1931.

4. Koch, S. L., cited by Mason, M. L.: Surg., Gynec. & Obst. **72**:250, 1941.

5. Levenson, S. M., and Lund, C. C.: J. A. M. A. **123**:272, 1943.

6. Berman, J. K.; Peterson, L., and Butler, J.: Surg., Gynec. & Obst. **78**:337, 1944.

7. Evans, E. I., and Hoover, M. J.: Surg., Gynec. & Obst. **77**:367, 1943.

. . . . In our experience, there is practically *no* external loss of plasma in 3d degree burns; the loss there is the "white hemorrhage" of Allen and Koch, plasma lost into the subcutaneous tissues under the burn. It is in the 3d degree burn that one sees the poorest results when tannic acid is used. To us it seems wholly illogical to cover the surface of a 3d degree burn with a heavy eschar to prevent plasma loss. The net result is no decrease in plasma loss.

Several unsolved problems exist in connection with the edema of burns. One problem considers the fate of the fluid and is discussed in this section under "Lymphatic Flow." Another relates to the possible toxicity of the fluid and will be discussed in the next section under "Toxic Factors."

Necrosis.—The importance of the depth of the burn is recognized by the various classifications of burns according to the penetration of the injury (Dupuytren, Boyer, Morton and others, reviewed by Harkins [8] in 1942). The recent work of Elman and Lischer [9] is of especial interest in this regard and presents several new points of view. These authors found three grades of damage to the skin: edema (produced by low temperatures or short exposure), wet necrosis (produced by medium temperatures and more exposure) and dry necrosis (produced by higher temperatures and longer exposure). They pointed out that the type of necrosis may be more important than its depth. Their observations were made on anesthetized animals but were correlated with clinical observations. They finally presented evidence that wet necrosis, even though a less severe injury than dry necrosis, may be more apt to lead to toxic and septic changes than the latter. Cellular infiltration, edema and other signs of inflammation were noted in the wet necrosis and not in the dry necrosis.

Another type of necrosis is that which appears as a result of trauma or of treatment received after the original burn. Pressure dressings as a method of local therapy protect the burned area from mechanical or septic trauma. On the other hand, it has been shown by Taylor [10] (1936), Cannon and Cope,[11] Hirshfeld, Pilling and Maun [12] (on man), Maun, Schneider, Pilling and Hirshfeld [13] (on dogs) and Clowes, Lund and Levenson [14] that other local remedies, tannic acid in particular, may increase the already existing necrosis of the skin and destroy remaining islands of skin.

Infection.—Infection is of importance in all deep burns. The present status of knowledge of such invasion is summarized in table 2.

Regeneration.—In this connection the most interesting recent work is that of Fell and Danielli.[16] Small shallow burns were produced on rats anesthetized with ether. The burns were made with a soldering iron 1.5 mm. in diameter, applied for about one second. Changes in the phosphomonoesterase of the skin were studied during the healing stage. Pooled scabs were analyzed, and the phosphatase content was estimated in terms of milligrams of chemically determined phosphate split off in a standard time. For the shallow burns tested such values were especially high during the stage of regeneration around the fifth day. The effects of various local agents on the regeneration of skin in burns has already been discussed under "Necrosis."

TABLE 2.—*Early Sepsis in Burns*

Cause.—Sepsis occasionally results from the action of flora resident in the skin; it often results from secondary contamination, especially with the hemolytic streptococcus, from unmasked and ungloved operators.
Time of Onset.—It usually appears after the fifth day. It may occur earlier (Aldrich [15]; Cruickshank,[19] 1935).
Treatment.—1. Administer sulfonamide compounds by mouth or parenterally. (The local application of easily absorbed sulfonamide compounds may cause toxic blood levels.)
2. Administer penicillin.
3. Change the position of the patient frequently to prevent pneumonia.
4. Of especial importance: Prevent sepsis by aseptic local treatment of the original burn with subsequent infrequent change of dressings during the first two weeks after the burn.

Lymphatic Flow.—The lymphatic flow from the burned area may act in two ways: to hasten the repair of the local area and to carry possible noxious products into the general circulation. Lassar [10] (1877) made experiments in which a hindleg of an animal was placed in water at 50 to 54 C. for five to six minutes, with resultant marked swelling. He reported that there was an increased flow of lymph in the scalded legs and expressed the belief that this was the mechanism whereby the fluid was reabsorbed and a return to normal effected. Wood [17] tested lymph specimens from the thoracic ducts of burned animals for vasodepressor activity by

8. Harkins, H. N.: The Treatment of Burns, Springfield, Ill., Charles C Thomas, Publisher, 1942.
9. Elman, R., and Lischer, C.: Surg., Gynec. & Obst. **78**:346, 1944.
10. Cited by Harkins.[8]
11. Cannon, B., and Cope, O.: Ann. Surg. **117**:85, 1943.
12. Hirshfeld, J. W.; Pilling, M. A., and Maun, M. E.: Surg., Gynec. & Obst. **76**:556, 1943.
13. Maun, M. E.; Schneider, R. C.; Pilling, M. A., and Hirshfeld, J. W.: Surgery **14**:229, 1943.
14. Clowes, G. H. A., Jr.; Lund, C. C., and Levenson, S. M.: Ann. Surg. **118**:761, 1943.
15. Aldrich, R. H.: New England J. Med. **208**:299, 1933.
16. Fell, H. B., and Danielli, J. F.: Brit. J. Exper. Path. **24**:196, 1943.
17. Wood, G. O.: Arch. Surg. **41**:1038, 1940.

injecting them intra-arterially into albino rats and observed no evidence of such activity.

Glenn, Peterson and Drinker [18] extended previous observations of Field, Drinker and White [19] on the lymphatic flow from scalded hindlimbs of anesthetized dogs. They noted a significant increase in lymphatic flow following the infliction of thermal trauma. A subcutaneous injection of tissue extract in the region of the burn caused coagulation of lymph, with stoppage of lymphatic flow. Sections of such an injected burned foot showed definite formation of fibrin while the noninjected burned foot showed practically no fibrin. In addition, a burned foot with injection of tissue extract tended to swell much more than a foot without such injection because "local swelling depends notably upon the degree to which coagulation of the exudate occurs with imprisonment of the water which leaks from the blood capillaries." Further evidence for this hypothesis is afforded by the observation that heparinization of the dogs to the extent that formation of fibrin was prevented was attended with minimal swelling of the foot after thermal trauma. Glenn, Muus and Drinker [20] studied the lymphatic flow from a scalded leg of a calf and compared the lymph as to amount and chemical composition with that from the opposite, untraumatized limb. The results were interpreted on the basis of the following logical assumptions:

> . . . We assumed that lymph coming from the burned area would contain a higher concentration of substances resulting from tissue damage due to the burn than would lymph from another part of the body, or serum taken from the general circulation. On the other hand, substances of small molecular size which accumulate in the serum owing to impaired function of any of the organs would be present in the same concentration in the serum and in the lymph collected from different parts of the animal.

Their studies seemed to indicate no increase in capillary permeability in normal regions of the body distant from the burn. They concluded that the increase in urea and creatinine was consistent with the usual observations attending oliguria. In their opinion the increase in creatine was due to local damage, while the increase in amino acid was of uncertain origin. (This observation concerning the rise in amino acid in shock due to burn fits in with the observations of Harkins, Long and associates.[21]) The rise in nonprotein nitrogen was just as great in the serum or the lymph from an unburned leg as in the lymph from the burned leg and hence does not seem to spring primarily from the region of local trauma.

18. Glenn, W. W. L.; Peterson, D. K., and Drinker, C. K.: Surgery **12**:685, 1942.

19. Field, M. E.; Drinker, C. K., and White, J. C.: J. Exper. Med. **56**:363, 1932.

20. Glenn, W. W. L.; Muus, J., and Drinker, C. K.: J. Clin. Investigation **22**:451, 1943.

GENERAL PATHOLOGIC CHANGES

The relationships between the local and the general effects of thermal trauma must always be kept in mind. Examples of this connection are too numerous to list completely, but a few are as follows:

(*a*) Effect of local loss of plasma in producing shock (Tappeiner,[10] 1881).

(*b*) Relationship between type of necrosis of skin and toxic changes (Elman and Lischer [9]).

(*c*) Effect of tannic acid in producing necrosis of the liver (Wilson [22]).

(*d*) Effect of pressure dressings in reducing loss of plasma and shock (Koch,[4] 1941).

Many of the general changes following burns are well understood; the etiology of others is less certain. In the following discussion the general trend will be to proceed from the known (e. g., hemoconcentration) to the unknown (e. g., toxemia).

Hematologic Factors.—The early hemoconcentration following burns, first noted by Baraduc [10] (1862), is so well known as to need no further comment. With the marked loss of plasma and resultant relative cell increase there is notable oligemia, possibly the most important of all general changes in burns. There is apt to be a relative decrease in albumin and chlorides, as well as a rise in potassium and other evidences of cell disintegration. The sedimentation rate is slowed early and hastened later. The white blood cell count is greatly increased in the early stages and remains high if infection supervenes. Transfusions of plasma or whole blood of an amount to fit the needs of the individual patient, calculated according to several methods reported in the literature,[8] are the chief form of treatment for hemoconcentration or rather for the oligemia of which hemoconcentration is a measure. The laboratory formulas of Harkins [23] or the nomogram of Jenkins, Schafer and Owens [24] may be used for this purpose. As

21. Harkins, H. N.; Long, C. N. H., and others: To be published.

22. Wilson, W. C.: Personal communication to the author, October 1938.

23. Harkins, H. N.: The Treatment of Burns with Particular Emphasis on the Management of Burn Shock, a brochure distributed in connection with the scientific exhibit at the meeting of the American Medical Association, in Cleveland, June 2-6, 1941.

24. Jenkins, H. P.; Schafer, P. W., and Owens, F. M., Jr.: Arch. Surg. **47**:1, 1943.

Evans [25] and others have emphasized, large infusions of plasma are often essential, and the clinical response, as well as empiric formulas, should serve as a guide to dosage.

Secondary anemia is a frequent occurrence after severe burns, in many cases coming on after the fifth day. It may be due to three chief causes: (*a*) reabsorption of fluid, (*b*) primary destruction or increased fragility of red cells due to the burn (Shen and Ham [26]) and (*c*) continued destruction of red cells and slowing of their formation due to sepsis, bleeding from granulating surfaces and malnutrition in the late stages. The treatment consists in administering blood transfusions, a high protein, high vitamin diet, iron and in some cases liver.

TABLE 3.—*Hypoproteinemia in Burns*

Cause.—Hypoproteinemia is of two types: early and late. The early type occurs in the shock phase, is rare and is often due to overtreatment with crystalloid solutions, given parenterally, or is associated with loss of plasma; it usually responds rapidly to treatment with plasma. The late type occurs in the granulating phase, is common and is due to metabolic protein imbalance, increased excretion of nitrogen in the urine, great loss of protein from the granulating surfaces and destruction of protein by accompanying infection.	
Time of Onset.—The early, rarer form occurs the first day or soon thereafter; the late, common form, during the period when granulating surfaces are present.	
Treatment.—1. See that the patient has a high protein diet. This is essential. The diet should include foods containing protein, and in severe cases amino acids should be given in addition by mouth or by jejunal tube and parenterally.	
2. Give transfusions of blood and plasma. The amount of protein that can be given in this form is small as compared with that necessary in severe cases.	
3. Institute adequate and prompt local measures to heal the wound and eliminate the cause of the hypoproteinemia. These include adequate supporting bandages and prompt skin grafting.	

Hypoproteinemia, especially when appearing late in the course of granulating burns, is an important condition to be reckoned with, as shown in table 3.

Hemoglobinemia and associated hemoglobinuria are often present during the first day or so after a severe burn. Shen and Ham [26] have shown that such hemoglobinemia usually results from direct trauma to red cells in the capillaries of the burned skin, while the precipitation of hemoglobin in the kidneys may contribute to the oliguria that often is noted. Lund [27] gave the following advice in this regard:

> . . . Patients with such [severe] burns should be catheterized at once and hemoglobin sought in the urine. Also the first blood specimen taken for hematocrit determinations should be used to test for hemoglobinemia. If either hemoglobinemia or hemoglobinuria are present, the patient should be alkalinized with intravenous injections of 40 cc. of 1 M lactate to each 500 cc. of plasma or an equivalent amount of sodium bicarbonate. As soon as an alkaline urine is established, the sodium lactate administration should be stopped.

Rosenthal [28] and Fox [29] also found alkaline solutions to be of benefit in burns.

Cardiodynamic Factors.—These are largely secondary to the oligemia and are not primarily due to cardiac or vascular failure. It is true that the experimental work of Simonart [10] (1938) on rabbits indicated that burns may cause marked electrocardiographic changes accompanied by pathologic alterations in the heart which include focal necrosis, calcification, some cellular infiltration and proliferation of connective tissue. Zinck [10] (1938), Fain [10] (1939), Gunther [10] (1939) and more recently Buis and Hartman [30] also noted cardiac changes following burns.

Essentially, however, the heart and the blood vessels are relatively unaffected, but the amount of blood they have to deal with is seriously depleted. Elman and Lischer [9] summarized the importance of the latter factor by stating: "The production of inflammatory edema alone is clearly the cause of loss of plasma leading to hemoconcentration, fall of blood volume, and the physical changes responsible for surgical shock." These cardiodynamic factors include decreased cardiac output, diminished blood flow, peripheral vasoconstriction, intact vasomotor center, decreased venous pressure and a late fall in arterial pressure. These items are all intimately interrelated and in turn are all essentially secondary to the oligemia. Abell and Page [31] studied the smaller blood vessels in anesthetized burned dogs and cats by direct vision. Vasoconstriction of the larger and smaller arteries and the larger veins and constriction of arteriovenous anastomoses were noted.

Septic Factors.—The septic factors represent a combination of local infection and general spread. Other conditions such as pneumonia may be of local or general causation or both. Thus, local damage due to inhalation of flames or hot air leads to pulmonary edema, which may become secondarily infected. In certain instances pulmonary edema (table 4) may also arise from a shocklike state. Walton [32] stated in this regard: "Tracheotomies in those patients who have inhaled fumes are essential and lifesaving. If there is any question as to the need for this operation, it should be carried out without delay." This

25. Evans, E. I.: Personal communication to the author, April 28, 1944.
26. Shen, S. C., and Ham, T. H.: New England J. Med. **229**:701, 1943.
27. Lund, C. C.: Rhode Island M. J. **26**:197, 1943.
28. Rosenthal, S. M.: Pub. Health Rep. **58**:513, 1943.
29. Fox, C. L., Jr.: J. A. M. A. **124**:207, 1944.
30. Buis, L. J., and Hartman, F. W.: Am. J. Clin. Path. **11**:275, 1941.
31. Abell, R. G., and Page, I. H.: Surg., Gynec. & Obst. **77**:348, 1943.
32. Walton, F. E.: Surgery **15**:547, 1944.

same author emphasized the general importance of sepsis in burns, stating: "Most of the patients with burns who die after a ten-day interval, die from sepsis."

Metabolic Factors.—These include a decreased metabolic rate in the presence of severe shock with resultant anoxic changes. The reviews of McClure [33] and Lam [34] give an especially good survey of these changes. Recent observations of Harkins, Long and associates [21] on this aspect of the subject are as follows:

In all instances burns (scalds) were produced by immersing white male rats of standard size in hot water of constant temperature for a definite period. From such an injury there resulted a rise in plasmic amino nitrogen, a slight rise in plasmic ammonia nitrogen, a slight rise in hepatic amino nitrogen, practically no change in hepatic ammonia nitrogen or hepatic amide nitrogen and no early decrease in oxygen uptake of liver slices but a late slight decrease as measured by the Warburg apparatus. The significance of these observations is best explained by correlating them with the observations of Engel, Winton and Long [35] on hemorrhagic shock. It is enough to say, however, that many of these changes appear to be of metabolic origin rather than directly produced by the burned area.

TABLE 4.—*Pulmonary Edema in Burns*

Cause.—Pulmonary edema usually occurs from (*a*) inhalation of flames or very hot air or steam, (*b*) inhalation of noxious gases released at the time of the burn (e. g., Cocoanut Grove disaster) and (*c*) more rarely, from a generalized increase in capillary permeability or from overtreatment with crystalloid solutions.
Time of Onset.—In cases with fulminating disease the lungs show edema after several hours; occasionally, after two or three days.
Treatment.—
1. Avoid excess fluids.
2. If coincident shock requires therapy, administer whole blood or, as next best, plasma. Crystalloids may be dangerous.
3. Turn the patient frequently.
4. Secure pressure breathing of oxygen.
5. Perform tracheotomy in selected cases.

The hypoproteinemia and associated negative protein balance often observed with late burns represent a type of metabolic disturbance. Such findings have been reported by Taylor, Levenson, Davidson, Browder and Lund [36] and by Cope, Nathanson, Rourke and Wilson.[37] These observations were made on the intake and output of protein alone, while Abbott,[38] working with Hirshfeld, found that the loss of nitrogen from the burned surface may be equal to 25 per cent of the total loss of nitrogen. One thus has another factor to consider.

Cope and associates [37] found in their cases of burn that the 17-ketosteroid excreted was elevated during the period corresponding to the negative nitrogen balance. This observation brings the subject of metabolic disturbances in burns to a consideration of a possible relation to endocrine factors, as discussed in the next section.

Endocrine Factors.—Early observations [10] were made indicating that damage of the adrenal glands is common in patients with burns. Cope and his associates [37] noted the increased excretion of 17-ketosteroid referred to. They also noted an abnormal growth of hair in the 6 women hospitalized for more than six weeks, despite a low level of 17-ketosteroid. These and other observations have suggested a possible endocrine disturbance in connection with burns. Recent work of Harkins and associates [21] has shown the presence in patients with burns of not only a disturbance of one gland but an interrelationship between two glands. After the production of standardized scalds in anesthetized rats there was a significant fall in the total cholesterol of the adrenal glands (e. g., from a normal concentration of 4.2 mg. per hundred grams of adrenal weight to as low as 0.7 mg.). This fall did not occur in hypophysectomized rats, indicating that the effect of the burn may not be directly on the adrenal gland but mediated by the pituitary gland, possibly by a stimulation of the production or the outpouring of adrenotropic hormone.

Toxic Factors.—There may well be toxic factors in burns, as the amount of damage and shock is not always sufficient to explain the accompanying morbidity and mortality. Such supposed toxins may act directly on various cells or organs or may affect them indirectly by means of concurrent metabolic or endocrine disturbances. The relationship between the degree of cutaneous damage and the possibility of toxemia was cited in the discussion of necrosis as an example of local pathologic change.

Rose and Browne [39] made studies on the blood histamine, the hemoglobin, the hematocrit reading and the plasma proteins following severe burns in 7 patients. They found in certain cases a definite increase in blood histamine within one

33. McClure, R. D.: J. A. M. A. **113**:1808, 1939.
34. Lam, C. R.: Surg., Gynec. & Obst. **72**:390, 1941.
35. Engel, F. L.; Winton, M. G., and Long, C. N. H.: J. Exper. Med. **77**:397, 1943.
36. Taylor, F. H. L.; Levenson, S. M.; Davidson, C. S.; Browder, N. C., and Lund, C. C.: Ann. Surg. **118**:215, 1943.
37. Cope, O.; Nathanson, I. T.; Rourke, G. M., and Wilson, H.: Ann. Surg. **117**:937, 1943.
38. Abbott, W. E.: Personal communication to the author, May 16, 1944.
39. Rose, B., and Browne, J. S. L.: Ann. Surg. **115**: 390, 1942.

hour after the burn. In all cases, however, there was a decrease in blood histamine with the appearance of toxemia and edema. With the disappearance of these two noxious signs and with clinical improvement of the patient, the blood histamine rose to normal or higher levels. In certain of their patients these secondary increases persisted for some time. Rose and Browne noted a definite correlation between the degree of damage and the decrease in the histamine of the blood. Thus, the greatest decrease was observed twelve to thirty-six hours before death. These authors finally observed that the changes in the histamine content of the blood do not appear to be altered by the administration of plasma in amounts sufficient to control hemoconcentration.

A summary of the therapeutic indications of toxemia in burns is given in table 5.

Recent observations of Prinzmetal, Freed and Kruger [40] and of Aub, Brues, Dubos, Kety,

TABLE 5.—*Toxemia in Burns*

Cause.—The cause is unknown in most cases. Tannic acid is a factor in some instances, but this is not the entire explanation. Necrosis of the liver is of especial frequency in patients treated with tannic acid.
Time of Onset.—Toxemia develops on the second to fifth day following the burn.
Treatment.—
1. Avoid tannic acid in readily absorbable form (jelly, bath). Rapid and infrequently repeated tanning is relatively safe, at least in this regard.
2. Control shock, sepsis and anemia.
3. Give adequate fluids to overcome oliguria and dextrose and protein to help protect the liver.

Nathanson, Pope and Zamecnik [41] have revived interest in the possible importance of infection in shock due to trauma of muscle. Previous work on this aspect of the subject included that of Mason and Davidson [42] (1925), Wangensteen and Waldron [42] (1928), Ellis and Dragstedt [42] (1929), Andrews and Hrdina [42] (1931), Trusler, Reeves and Martin [42] (1934), Harkins, Harmon and Hudson,[43] Moon [44] and others. All of this work emphasizes the possibility that the role of bacteria in the toxemia associated with clinical burns (as stressed by Aldrich [15] and by Firor [45] in 1933) may be of importance. On the other hand, the work of all these other investigators almost invariably was on dogs, whose tissues normally may contain gas-forming bacilli. Such work may not be applicable without reservation to human beings or to shock caused by burns.

The recent observations of Pfeiffer, Hallman and Gersh [46] on the toxicity of boric acid ointment used in the treatment of burns are of especial interest. These authors tested the ointment on dogs and found that "treatment of a burn involving only 4 per cent of the surface area of the body with U. S. P. 10 per cent ointment, will produce pathological changes in the central nervous system." These authors concluded as a result of their work:

> . . . Boric acid, whether applied in the form of an ointment or a saturated solution to extensive wounds is a cumulative poison. The weak antiseptic value of boric acid suggests that for most uses, other more active and less potentially harmful therapeutic agents should be employed.

This work on the toxicity of boric acid repeats an old lesson in the history of the therapy of burns, one noted before, in the case of trinitrophenol (picric acid), and later, in that of the tannic acid treatment. This is that each time man attempts to become more elaborate and use anything other than the simplest of coverings on an extensive burned surface, he is apt to do more harm than good.

SUMMARY AND CONCLUSIONS

Burns do not produce a simple combination of local damage with secondary remote effects. Actually, severe thermal trauma throws the whole regulatory mechanism of the body out of gear. Local edema leads to oligemia with hemoconcentration and other hematologic and cardiodynamic changes. Increased lymphatic flow may help in the local repair, and it may carry off toxic products which may produce general damage. Local necrosis and infection delay regeneration and lead to general sepsis. In addition, certain bits of evidence indicate that the entire metabolic and endocrine adjustment of the burned patient may be altered. Certain of these many changes respond readily to therapy; thus the oligemia is overcome by the administration of plasma. Other alterations in the light of present knowledge are still self limited. All of these observations indicate the importance of considering the burned patient as a whole rather than as a collection of parts.

40. Prinzmetal, M.; Freed, S. C., and Kruger, H. E.: War Med. **5**:74, 1944.

41. Aub, J. C.; Brues, A. M.; Dubos, R.; Kety, S. S.; Nathanson, I. T.; Pope, A., and Zamecnik, P. C.: War Med. **5**:71, 1944.

42. Cited by Harkins and associates.[43]

43. Harkins, H. N.; Harmon, P. H., and Hudson, J. E.: J. A. M. A. **107**:948, 1936.

44. Moon, V. H.: Shock: Its Dynamics, Occurrence and Management, Philadelphia, Lea & Febiger, 1942.

45. Firor, cited by Aldrich.[15]

46. Pfeiffer, C. C.; Hallman, L. F., and Gersh, I.: A Study of Possible Intoxication from the Use of Boric Acid Ointment in the Treatment of Burns, Special Report, Naval Medical Research Institute, Bethesda, Md., April 4, 1944.

DISCUSSION

DR. CONRAD R. LAM, Detroit, Mich.: I must differ with Dr. Harkins as to the credit for priority in the demonstration of the toxic effect of tannic acid on the liver. I should like to ask him if it is not true that although the patients whose cases were reported by W. C. Wilson and his associates in 1938 were treated with tannic acid, these authors did not hint that the method of treatment might be an etiologic factor in some of the fatalities. The first public incrimination of tannic acid was made by Dr. Donald B. Wells, of Hartford, Conn., at the meeting of the American College of Surgeons in 1940, and this work was published in April 1941.

A short time ago, Dr. Roy D. McClure, Dr. Howard Romence and I wrote a paper entitled "The Tannic Acid Treatment of Burns: An Obsequy," which was read at the meeting of the American Surgical Association. It was our hope that this method of treatment would be abandoned. In spite of considerable publicity, some physicians are still treating burns with tannic acid, a fact which came to light in the discussions at the exhibit on burns in the Scientific Exhibit.

In the paper read at the meeting of the American Surgical Association we stated that we had never seen a lesion of the liver comparable to that in the patient who had not been treated with tannic acid. In response to this statement, Dr. Evans, of Richmond, Va., sent some sections of livers from patients not treated with tannic acid, and these showed considerable central necrosis. However, since a sulfonamide compound had been used in local treatment, we are still of the opinion that the lesion of the liver in cases of burns is due to some chemical substance which has been applied externally.

DR. H. PERRY JENKINS, Chicago: There is a point which I should like to raise in this discussion which undoubtedly influences the magnitude of cutaneous necrosis in burns. This point is the using of solvents such as benzene or other similar hydrocarbons to remove dirt and grease from a burned area before applying the petrolatum or other dressing for the burn. Benzene is capable of producing a chemical burn of normal intact skin. The irritant and necrosing effect of benzene on partially denuded areas of skin should not be underestimated. Some idea of the magnitude of the irritant action in the tissues of solvents such as benzene can be obtained from intradermal skin tests with minute amounts of these solvents in dilution. In tests with solvents related to benzene, such as xylene and high flash solvent, which incidentally were found to be present in certain kinds of catgut tubing fluid, it was found by Dunham and me that as little as 0.00025 cc. of these substances was capable of producing a detectable inflammatory lesion. Higher concentrations were capable of producing necrosis. In view of the extremely potent irritant action of solvents of the benzene group when introduced into the tissues it would appear that the use of such solvents on burned skin is undesirable because it may superimpose a chemical burn on a thermal burn and possibly destroy remaining viable epithelium which has escaped the thermal trauma. Thus a second degree thermal burn may be converted into a third degree burn by the preliminary treatment.

Attention should be drawn to the many surface-active agents which have detergent properties and which can be used to remove grease. These can be used in 5 to 15 per cent concentrations in water, and although they may not be entirely free from tissue-irritant properties, the magnitude of such irritant properties is remarkably less than that of the solvents of the benzene group.

DR. VIRGIL H. MOON, Philadelphia: Several features of burns would have merited longer consideration had time permitted. Probably Dr. Harkins would have mentioned important metabolic disorders and evidence of systemic disturbances. Prominent among these is deficiency of renal function. This is manifested by oliguria and deficient renal excretion promptly after severe burns, and it remains a major clinical factor during the first few days or until recovery is well advanced.

This item has not received the attention from clinicians which it merits. When a severely burned patient is brought in, the doctor's attention is absorbed by emergency measures, the local treatment of the burned area and the prevention of circulatory failure. Often he may not observe evidences of renal deficiency or, if he does, probably there is nothing to do about it. But that deficiency is a factor in burns as well as the feature of disturbed hepatic function.

There is agreement that after death from burns the liver shows marked damage, but it is doubtful that this is due entirely to the chemotherapy. Reviews of the literature on burns by Bardeen in 1897 and by Pack in 1926, before the days of chemotherapy, indicate that extensive hepatic necrosis is one of the usual results of burns.

Some of us believe that both the hepatic and the renal damage are evidences of a systemic toxic effect, which effect has not received due recognition or emphasis. I am gratified to note that Dr. Harkins and others now recognize systemic effects and agree that not all of the disturbances resulting from burns are due solely to local effects, such as trauma, loss of blood and fluid, and infection.

DR. EVERETT IDRIS EVANS, Richmond, Va.: Infection is the nemesis of all successful treatment of burns. It is one of the main contributors to serious local pathologic developments. The practical significance of this is not how infection is best treated but rather how it is best prevented.

Although others have suggested that the careful cleansing of burned areas with copious quantities of sterile soap and water may be considered an unnecessary step in the treatment of a burn, the experience of the group with which I am associated in a large series of severe burns is that where this has been done routinely it has yielded gratifying results. There still exists controversy as to the wisdom of using sulfonamide compounds on burned surfaces. Again our experience, coupled with that of Ackman and Gurd and Andrus and Dingwall, has convinced us of the wisdom of this policy. If we combine the large series of burns treated by Ackman and Gurd with our own series, the severe burns thus treated number now somewhat over 400. The incidence of infection in this combined group of burns has been exceedingly low. It should be stressed here that both the Montreal and the Richmond group have used a sulfonamide compound which was prepared in such a manner that low blood concentrations of the substance resulted even when it was used on large burned surfaces. If a so-called "water base" is used in the sulfonamide preparation, the blood levels of the sulfonamide compound will be high.

With the combination of proper masking and aseptic care of hands and instruments, careful washing of the burned areas with soap and water and the use of oily ointments containing sulfonamide compounds, infection in severe burns has practically ceased to be a serious problem.

If one combines with this an occlusive dressing with the proper pressure and takes care to remove these dressings only after a long period of time (about fourteen days), secondary infection of any surgical significance at the site of the burn will not occur.

We are inclined to agree with what Dr. Harkins has told you of the dangers of tannic acid and of escarotics in causing additional local damage when they are placed on a burned surface.

There can be little doubt that tannic acid produces in certain patients and experimental animals severe hepatic damage. Those who have gone over much pathologic material from patients who have died of burns after treatment with tannic acid have found that as regards many such patients little evidence of the hepatotoxic action of tannic acid can be noted.

Severe avitaminosis may be present in badly burned patients. Three burned patients were referred to us recently who all showed evidence of rather marked deficiency of prothrombin due, we believe, to poor dietary intake of vitamin K.

I am not convinced that secondary shock following burns can be explained simply on the basis of loss of plasma, since in our own series there have been patients who had severe depletion of plasma volume yet showed no shock.

Dr. Henry N. Harkins, Baltimore: Unfortunately, Dr. Lam did not have my paper or he would have seen that my reference to Wilson's statement concerning the toxicity of tannic acid, in the bibliography, was a personal communication. In other of my writings I have given Wells, of Hartford, Conn., full credit for the first written report of the toxicity of this substance for the liver.

I should like to emphasize one other point that has not been mentioned, namely, that tannic acid is more toxic in certain forms than in others. This is especially true of the jelly, from which there is a chance of absorption over a period of many thousands of seconds, whereas when tannic acid is dried immediately or is applied in the form of tannic acid-silver nitrate, there is a chance of absorption in the moist form over only a few seconds.

I agree with Dr. Jenkins that the possibility of toxicity of other medicaments is always to be considered. Each time man attempts to become more elaborate and use something other than the simplest of coverings on an extensive burned surface, he is apt to do more harm than good.

I agree with Dr. Moon that the renal insufficiency is of great importance, and in many fatal cases anuria or a decrease of renal excretion occurred some time or other during the course of the illness.

The hepatic changes that follow the application of tannic acid are a little different from those that occur when burns are not treated with tannic acid. But I agree that burns not treated with tannic acid can produce severe hepatic changes. I am also convinced that toxemia does occur in burned persons whether or not it accompanies other types of shock.

The importance of infection, emphasized by Dr. Evans, is self evident, especially his pointing out that, even though the resident flora may not be entirely removed, this does not mean that one should not make every attempt to prevent introducing new and possibly more noxious bacteria from the nose and throat of the operator.

The point that certain types of burns are apt to be more toxic than others is somewhat in agreement with Dr. Elman's recent paper that the necrosis in burns is apt to be of either a wet or a dry type and that the toxemia is much more apt to occur following wet than following dry necrosis, just as it does with any other type of gangrene.

ADENOMA OF APOCRINE SWEAT GLANDS (HIDRADENOMA) OF THE ANAL CANAL

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AND
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The anorectal outlet is formed by the junction of the ectodermal proctodeum with the entodermal rectum. The anorectal blood vessels, lymphatics and supportive structures are derived from mesoderm. Thus the three primary embryonic layers participate in the development of structures in this region.

The length of the anal canal varies from 1.5 to 3 cm.; the average length is about 2.5 cm. The internal boundary is the pectinate line or the dentate margin. The external limit of the anal canal is at the anal verge. The walls of the anal canal are lined by modified squamous epithelial cells. These points are significant in considering the cause of anorectal disease and its development and extension.

In the anal canal there are two types of sweat glands, the eccrine or ordinary sweat glands and the apocrine sweat glands.

The study of apocrine glands dates back to 1846, when Horner [1] described glands of the axilla which he named odoriferous glands (apocrine). In 1854 von Kölliker [1] said that the cells of apocrine glands contain much more protein and fat than do ordinary sweat glands (eccrine glands). In 1922 Schiefferdecker [1] again called attention to the eccrine and apocrine types of sudoriferous glands. Way and Memmesheimer [2] have adequately described the development of the apocrine glands as follows:

> The apocrine gland, together with the sebaceous gland and the hair follicle, develops from the primary germ of the epithelium and is the first form to separate. It is therefore formed from already differentiated epithelium, while the eccrine type develops from undifferentiated epithelium.
>
> After the formation of the gland the distal end of the duct may wander from the hair follicle to empty on the free surface of the skin. The excretory orifice of the eccrine gland, however, never opens into a hair follicle. . . . Apocrine glands can be found only where hair exists or has existed.

Apocrine sweat glands are situated deeply in the dermis and can be recognized grossly by their reddish hue. According to Way and Memmesheimer, the glomerulus of the apocrine sweat gland is 3 or 4 mm. in diameter and is a tube loosely rolled on itself with alternate regions of narrowing and dilatation. This tube, the diameter of which varies from 100 to 200 microns, has a wide lumen lined by two layers of cells. The basal layer of cells is approximately 2 microns thick. This layer of cells is usually referred to as the myoepithelial layer, and it tends to form a continuous internal ring that acts as a support to the secreting cells which line the lumen. The secreting cells which form the internal layer vary from 24 to 36 microns in height, depending on whether they are actively secreting or resting. The nuclei are rounded and are situated centrally when the cells are in the resting stage but move toward the base when the cells are secreting actively. The cytoplasm is filled with yellowish pigment and is strikingly eosinophilic. It often is shaped so that it projects into the lumen of the gland.

The apocrine glands do not function until the sex glands mature. When secretion occurs in apocrine glands, there appears to be an accumulation of granules near the surface of the cell and a part of the cell itself is lost during secretion.

Richter [1] expressed the belief that apocrine glands lead in secretion of cholesterol. Way and Memmesheimer [2] stated that there is reason to believe that apocrine glands occur twice as frequently in women as they do in men, that they are not decreased numerically in old age and that they become enlarged in pregnant women, especially in those who have eclampsia. Way and Memmesheimer [2] expressed the belief that apocrine glands function from the beginning of sexual maturity and continue to function until old age. In women their function is reduced during the intermenstrual period but increased in the premenstrual period. The function also is increased during pregnancy, when hypertrophy and hypersecretion occur. These glands are true "accessory sexual glands."

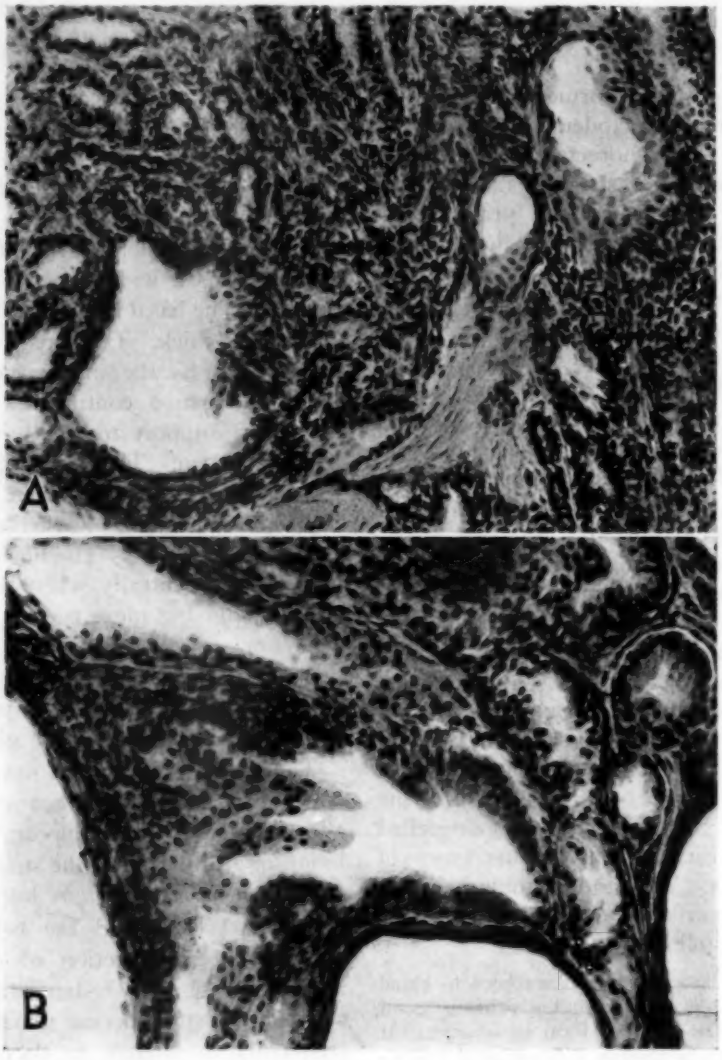
From the Section on Surgical Pathology, Mayo Clinic.

1. Cited by Way and Memmesheimer.[2]

2. Way, S. C., and Memmesheimer, A.: Arch. Dermat. & Syph. **38**:373, 1938.

Brinkmann [1] expressed the belief that the odor of the secretion of apocrine glands increases sexual excitement.

The apocrine sweat glands are even more interesting from the standpoint of the pathologic changes.



A, hidradenoma of the anal canal; this portion of the tumor shows cells with hyperchromatic nuclei and imperfectly formed acini (× 170). *B*, another section of the neoplasm shown in *A*. There are well formed glands lined by cells exhibiting a free border of cytoplasm and papillary infoldings. These glands resemble apocrine sweat glands (× 200).

In 1904 Pick [3] described 2 tumors which appeared to him to take their origin from rudimentary sweat glands. He expressed the opinion that the tumors were adenomas, and he demonstrated their connection with sweat glands. He coined the term "hidradenoma." In each case the tumor was excised from the vulva. Hoeck,[4] Blau [5] and Woringer [6] each reported a case of hidradenoma of the vulva. Burg [7] in 1930, while reviewing the literature, found that 15 cases of hidradenoma of the vulva had been reported, and he added a case of his own. In all but 2 cases the tumor was considered noncancerous. One of these 2 cases was reported by Ruge [8] in 1905, and the other was reported by Schiff-

3. Pick, L.: Virchows Arch. f. path. Anat. **175**:312, 1904.

4. Hoeck, W.: Zentralbl. f. Gynäk. **50**:2757, 1926.
5. Blau, A.: Ztschr. f. Geburtsh. u. Gynäk. **93**:341, 1928.
6. Woringer, F.: Bull. Soc. franç. de dermat. et syph. **45**:112, 1938.
7. Burg, E.: Zentralbl. f. Gynäk. **54**:395, 1930.
8. Cited by Burg.[7]

mann[8] in 1920. In 1933 Ullmo[9] reported a case in which hidradenoma of the breast was encountered in a woman 35 years old. In the same year, Sézary and Lévy-Coblentz[10] reported the occurrence of hidradenoma on the forehead of a white woman aged 44 years. Eichenberg[11] in 1934 reported 12 cases of papillary adenoma of the vulva. In these cases he found dilated cystic sweat glands around the adenoma and expressed the belief that the adenoma originated from them. In 1 case he found evidence that the tumor was cancerous.

In 1935 Montgomery[12] pointed out that even true metaplasia may occur in cells of the epidermis that have begun to differentiate toward sweat ducts. He also stated that the basal cells that line the outer sheaths of the hair follicles, the sweat ducts and the sebaceous glands are similar to the basal cells of the epidermis and therefore may participate independently or simultaneously in any neoplastic process.

Rothman and Gray[13] in 1939 reviewed 37 cases of hidradenoma of the vulva reported in the literature and added 5 cases of their own. They stated that hidradenoma is noncancerous and usually is situated on the labium majus and that there may be more than one tumor in the same case.

One of us (McDonald[14]) in 1941 presented the first description of a neoplasm whose origin could be definitely traced to an apocrine gland. He studied 30 such vulvar neoplasms which he considered to be slowly growing carcinomas. Many of these neoplasms could be shown to arise from apocrine sweat glands. German authors who described such tumors did not state specifically that they came from apocrine in contradistinction to eccrine or ordinary sweat glands. The case which we shall report is believed to be the first reported case of a neoplasm of the anus arising from apocrine sweat glands.

REPORT OF A CASE

A white woman aged 42 years, married, first came to the Mayo Clinic on Feb. 2, 1924, because of pain in the right side of her abdomen. The pain was of a dull aching character, situated all along the right side of the abdomen, and had occurred intermittently for the past nine years. It was not associated with eating any particular food but was relieved by bowel movements. Invariably the attacks of pain had been followed by dysentery. Occasionally the pain had been accompanied by nausea but not by vomiting. The attacks of pain had become more frequent until the pain had become constant. There had been no jaundice, chills or fever.

She was a well nourished, well developed white woman. Her blood pressure was 138 mm. of mercury systolic and 76 mm. diastolic. The pulse rate was 72 and the temperature 98 F. The eyes, the ears, the nose, the throat and the thorax were normal. There was severe tenderness on palpation over McBurney's point, and a lesser grade of tenderness was present in the right upper quadrant of the abdomen over the region of the gallbladder. A pelvic examination revealed laceration of the cervix, rectocele and cystocele; the uterus was normal.

Examination of the rectum disclosed hemorrhoids. A small cyst also was found just external to the anal orifice.

On February 19 appendectomy and cholecystectomy were done. The patient made an uneventful recovery. The pathologic report was chronic catarrhal cholecystitis and chronic appendicitis.

On March 15 the lacerated cervix was repaired, perineorrhaphy was performed, the hemorrhoids were removed and the cyst just external to the anus was removed.

The cyst of the anus was observed to be covered with squamous epithelium, and within the cyst was a papillary tumor. The cyst measured 1.5 cm. in diameter. The tumor was made up of glands with papillary projections (figure). Some of these glands were lined by cells which were eosinophilic and answered the description of apocrine sweat glands. It was possible to demonstrate a transition between the epithelium typical for apocrine sweat glands and the regular epithelium of the neoplasm. Mitotic figures could not be demonstrated.

COMMENT

Apocrine sweat glands rarely become diseased; the only neoplasm which has been demonstrated as originating from apocrine sweat glands is hidradenoma. It is believed that the breast is developed from apocrine sweat glands, and, if this is true, it is possible to consider many of the diseases of the breast as originating from modified apocrine sweat glands. In many instances the so-called intraductal papilloma of the breast bears a striking morphologic similarity to adenoma of the apocrine sweat glands (hidradenoma). Although there is some evidence to support the idea that neoplasms of this type are histologically cancerous (invasion, morphologic aspects and so forth), there is little clinical evidence to support it. Metastasis has not been demonstrated. Surgical removal seems to effect a cure.

9. Ullmo, A.: Bull. Soc. franç. de dermat. et syph. **40**:1098, 1933.

10. Sézary, A., and Lévy-Coblentz, G.: Bull. Soc. franç. de dermat. et syph. **40**:224, 1933.

11. Eichenberg, H. E.: Ztschr. f. Geburtsh. u. Gynäk. **109**:358, 1934.

12. Montgomery, H.: Radiology **25**:8, 1935.

13. Rothman, D., and Gray, S. H.: Am. J. Obst. & Gynec. **38**:509, 1939.

14. McDonald, J. R.: Am. J. Clin. Path. **11**:890, 1941.

Case Reports

CAPILLARY HEMANGIOMA OF BONE

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With the work of Makryocostas [1] and Töpfer [2] it was shown that hemangioma of bone, particularly of the spine, is a more common lesion than had been thought. Töpfer found hemangioma in 11.9 per cent of 2,154 spines examined at autopsy. In 9 of the cases hemangioma was present also in other bones. However, since no symptoms were produced in any of these cases, hemangioma of bone remained a pathologic curiosity and reports of cases were few.

In 1930 the important paper of Bucy and Capp [3] on primary hemangioma of bone presented the pathologic and roentgenographic features which are now considered to be typical. The literature was reviewed by these authors and they presented 35 cases on which to base their conclusions. In 1938 Geschickter and Maseritz [4] reviewed the literature to that date and added 2 cases. In 1942 Thomas [5] reviewed the 11 benign vascular tumors of the Bone Sarcoma Registry and added 1.

Recently interest in hemangioma of bone has increased, particularly since it has been realized that hemangioma of the spine can be responsible for the symptoms of cord compression. There have been reports of some 60 cases, all told, not all of which are well confirmed.

In two thirds of these reported cases the lesion was located either in the spine or in the skull. In one fourth of the cases it was in the long bones. Among the remaining cases there were 2 in which the tumor was in the pelvis, 2 in which it was in the tarsal bones and 1 in which it was in the scapula.

The pathologic observations in almost all of these cases are similar and are those of typical cavernous hemangioma. Among all the varied reports there can be found records of only 4 cases in which the hemangioma was thought to be of the capillary type. No. 849 of the Bone Sarcoma Registry, photomicrographs of which appear in the paper of Bucy and Capp,[3] is a capillary hemangioma of the ulna in a 24 year old soldier. Kümmel [6] reported a capillary hemangioma of the nose, maxillary sinus and skull. Geschickter and Maseritz [4] reported such a lesion in the humerus, and Abbott [7] reported one in the skull.

In view of the rarity of this type of lesion and because the roentgen findings differ widely from the description given by Bucy and Capp [8] it is thought worth while to present a fifth case.

REPORT OF A CASE

At birth J. R. appeared to be a normal child. In October of 1937, when she was a month old, her mother brought her to the clinic because it had been noted since a few days after birth that her left knee was swollen. Examination disclosed only that the left knee was 1 cm. greater in circumference than the right. When the child was 8 weeks old, a roentgenogram was made which showed no lesion of bone but a definite soft tissue swelling. The swelling gradually decreased, and by the time the child was 5 months old, according to the record, there was "only a slight dimpling at the site of the former sclerema."

In March of 1939, when the patient was 18 months old, she was brought back because the parents noted that she "slapped" her left foot as she walked. There were no findings except that the left knee was now 2 cm. greater in circumference and the extremity 1 cm. longer than the right (fig. 1 *A*). Five months later the child complained of occasional pain in the knee, and a slight flexion contracture developed. At this time the relative dimensions of the extremities had not changed and there was no abnormality in auscultation over the femoral vessels, but a roentgenogram showed an area of radiolucency in the anterior portion of the lower part of the femur and periosteal elevation for about 6 cm. up from the epiphysial line.

By January of 1940, when the patient was 2 years and 4 months old, more sclerosis and more periosteal new bone were visible on the roentgenogram (fig. 1 *B*). On January 19, with a preoperative diagnosis of osteomyelitis, the lesion was explored. Organized periosteal new bone was encountered for some 5 cm. up from the epiphysial plate. The cortex was thickened over a slightly greater area, and the medullary cavity was full of sclerotic cancellous bone. As much of this as could

From the Department of Surgery, Division of Orthopedic Surgery, University of Chicago.

1. Makryocostas, K.: Virchows Arch. f. path. Anat. **256**:259, 1927.

2. Töpfer, D.: Ueber ein infiltrierend wachsendes Hämangiom der Haut und multiple Kapillarektasien der Haut und inneren Organe. Zur Kenntnis der Wirbelangiome, Frankfurt. Ztschr. f. Path. **36**:337, 1928.

3. Bucy, P., and Capp, C.: Am. J. Roentgenol. **23**: 1, 1930.

4. Geschickter, C., and Maseritz, F. H.: J. Bone & Joint Surg. **20**:888, 1938.

5. Thomas, A.: Surg., Gynec. & Obst. **74**:777, 1942.

6. Kümmel, W., and Rockemer, K.: Monatschr. f. Ohrenh. **64**:1368, 1930.

7. Abbott, W. D.: Ann. Surg. **113**:306, 1941.

8. "In cylindrical bones the tumor is loculated. These loculations are small with an interspersed fine fibrillary framework. The cortex is usually destroyed but may extend into the center of the expansive tumor. The periosteum, though expanded, remains intact."

be removed without danger of predisposing to fracture or to arrest of growth was curetted out. Anteriorly several pockets of fibrous tissue were removed. No pus was found, and the wound healed by primary intention.

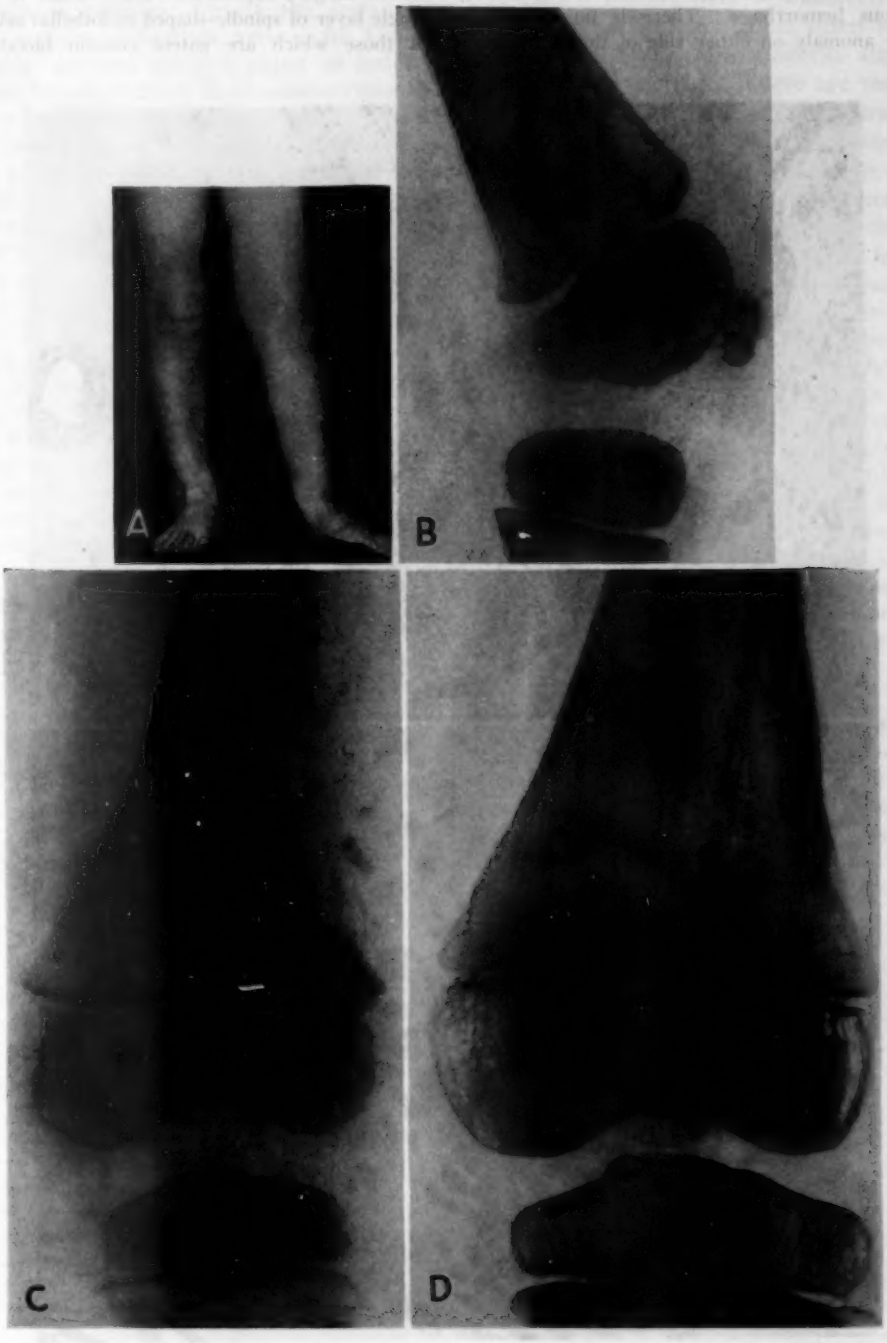

Fig. 1.—*A*, photograph showing knees of the patient at the age of 18 months, *B*, preoperative roentgenogram. *C*, roentgenogram taken immediately after operation. *D*, roentgenogram taken twenty-three months after operation.

Cultures made in the operating room produced no growth (fig. 1 *C*).

In June of 1940 the patient still had symptoms (pain and limp), although she was improved and the roentgenogram showed good healing of the operative defect. The left leg was 3 cm. longer than the right. By July of 1941, eighteen months after operation, the patient was asymptomatic and the roentgenogram showed the defect in the femur to be healed (fig. 1 *D*). In January of the following year she had a brief return of pain and tenderness, which subsided spontaneously and which were not accompanied by physical or roentgenographic changes.

In July of 1944 she had been completely free of pain for twenty-three months. There was still 1.5 cm. difference in the length of the left leg, which was due to

overgrowth of the left femur. The patient compensated perfectly for this and walked without a limp.

This child has a negative cutaneous reaction to tuberculin. She has no cutaneous nevi, and her fundi are normal. She has never had headaches, convulsions or spontaneous hemorrhage. There is no history of any vascular anomaly on either side of the family.

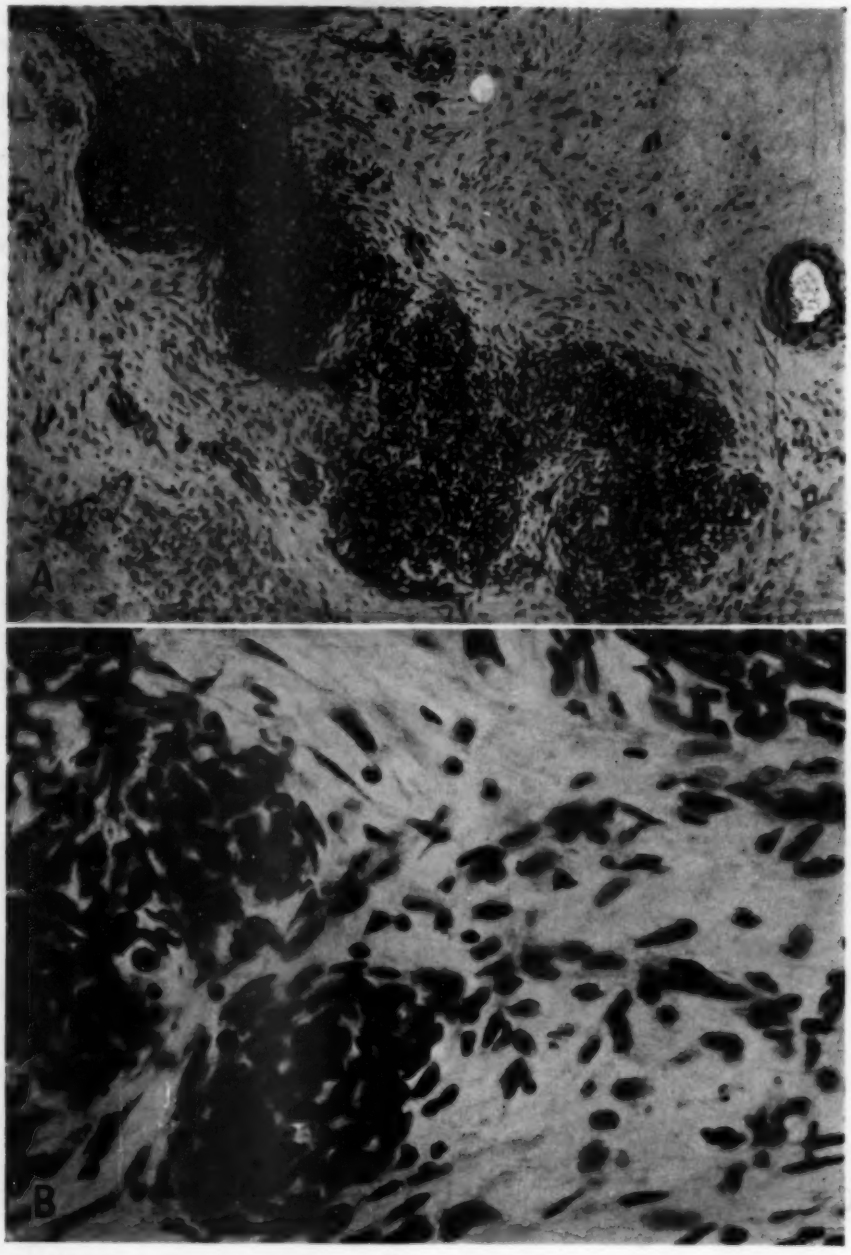

Fig. 2.—*A*, low power photomicrograph. *B*, high power photomicrograph.

The sections of the material removed at operation show hypertrophic cancellous bone with active bone formation. At the edges of the lesion the marrow is fatty and edematous and contains loose strands of fibrous tissue. There is an occasional island of normal hemopoietic elements. Toward the center of the lesion the bone is more hypertrophied and new bone formation more striking. The marrow is entirely replaced by densely organized fibrous tissue, which contains numerous well defined tumor nodules (fig. 2*A*). Each of these nodules is composed of a knot of closely interwoven tangled capillaries. Each vessel is lined with a single layer of spindle-shaped endothelial cells, and many of those which are patent contain blood. Scattered among the capillaries but always lying between them are pale giant cells with 6 to 10 nuclei (fig. 2*B*), which may represent fusion of several endothelial cells. Between the vessels in the tumor nodules there is almost no stroma, but at the border of the nodules there is sometimes a blending of capillaries into the surrounding fibrous tissue. No mitotic figures are

seen, and there is no evidence of inflammatory reaction. There are no intracellular deposits of fat or of hemosiderin.

If a lesion is typical capillary hemagioma, the diagnosis is obvious, but if the lesion is regressing, certain difficulties arise. As Gross and Wolbach [9] pointed out in a paper on lesions of soft tissue, hemangioma is in all cases composed of blood vessels and fibrous tissue. In some cases the fibrous stroma exhibits a tendency to proliferate at the expense of the blood vessels. The vessels may be surrounded and compressed by the fibrous tissue and eventually completely closed. When this happens, groups of endothelial cells may be isolated and may coalesce to form giant cells, which Gross and Wolbach observed in 15 of 67 cases. They noted also that intracellular deposits of fat and of hemosiderin were seen in about three fourths of their cases, sometimes to the extent that xanthoma and melanoma were difficult to rule out. They expressed the opinion that all of these changes were part of a spontaneous regression that ultimately results in a dense connective tissue scar in which there may be no identifiable vascular elements.

Other lesions of soft tissue which have a rich blood supply may resemble capillary hemangioma. This is especially true of the type of infectious process which is sometimes called granuloma pyogenicum, which can present areas composed of nothing but well formed capillaries with much intracellular hemosiderin. However, inspection will disclose in different parts of the same lesion areas of necrosis, collections of inflammatory cells and other evidence that infection is the primary disease and that the capillaries are part of the vascular response of repair.

A similar picture may be observed in solitary eosinophilic granuloma. One often sees islands of capillaries, much hemosiderin and small or large areas of necrosis. There are many inflammatory cells, often so-called xanthoma cells, and in these foci there is a spectacular concentration of eosinophilic leukocytes. Here again the capillaries appear to be part of a local response to another primary process rather than responsible for the development of the lesion.

In the lesion under consideration there are only two components: fibrous tissue and blood-containing capillaries. The capillaries appear to be the basis of the lesion, and they are actively proliferating. There is no evidence of inflammation or of infiltration with other cells.

The histologic picture, the history of symptoms since birth, the relief of symptoms by operation in which the lesion was incompletely excised and the fact that there has been no recurrence or spread confirm the impression that this lesion is a congenital capillary hemangioma, primary in the lower part of the femur, which is undergoing fibrous regression or "sclerosis."

SUMMARY

A child since birth had had pain and swelling of the lower part of the thigh. Roentgenograms showed a destructive lesion of the distal femoral metaphysis. Relief of symptoms followed curettage. Sections showed the lesion to have been a capillary hemangioma.

9. Gross, R. E., and Wolbach, S. B.: Am. J. Path. **19**:533, 1943.

General Reviews

ARTERIOSCLEROSIS

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INTRODUCTION

The degenerative and sclerosing arterial diseases known under the collective term of arteriosclerosis are becoming increasingly important in medical, medicolegal, hygienic, social and economic respects because of the rapid rise in the number of old persons in the population in all civilized countries and the constantly growing exposure of the general population to exogenous arteriosclerotogenic agents forming a part of the new industrial environment. The urgent significance of this development is accentuated by the general uncertainty in regard to the nature of and the relationship between the etiologic factors, the causative mechanism and the morphologic aspects of these chronic disabling vascular diseases, by the thereby conditioned lack of adequate diagnostic methods and of rational and effective preventive and therapeutic measures and by the additional shift toward the older age groups brought about by the present war.

This unsatisfactory condition is in part attributable to the fact that among the various theories of arteriosclerotogenesis none has found wider acceptance or remained in general favor over a longer period than the senescence theory. Because of the undue emphasis on physiologic senescing processes, the solution of the problem of arteriosclerosis has remained for many years in a state of scientific stagnation, a state shared until rather recent years by the problem of cancer, another so-called disease of old age. The mental attitude which developed toward the problem of arteriosclerosis under the influence of the senescence theory is perhaps best characterized by citing the following statement of L. Aschoff: "If arteriosclerosis were merely a phenomenon of aging, neither remedies nor prophylactics would be of any avail, for no one can escape age and death."

It therefore appears pertinent that the various theories should be critically analyzed and their respective merits determined in the light of the available biologic, pathologic and experimental data properly systematized and integrated. Such an evaluation is essential for the future development of scientifically sound preventive, prophylactic and therapeutic measures derived from a clear understanding of the numerous etiologic factors, their different causative mechanisms and the various anatomic vascular lesions produced by them.

From the Warner Institute for Therapeutic Research.

THEORIES OF ARTERIOSCLEROTOGENESIS

Any theory of the genesis of arteriosclerosis which lays claim to be generally valid must provide plausible explanations for the following facts: 1. The not infrequent absence of appreciable arteriosclerotic lesions in persons of advanced age. 2. The not unusual occurrence of degenerative as well as sclerosing arterial changes in young and, occasionally, very young persons. 3. The absence of arteriosclerosis with age in certain species of animals and its relatively early appearance in some other species. 4. The common irregular topographic involvement of the arterial tree by these changes. 5. The pronounced differences in anatomic types of arterial lesions and their dependence on certain structural vascular peculiarities or locations. 6. The definite relation of certain degenerative and sclerosing vascular manifestations to sex and possibly also to race. 7. The obvious connection of these vascular changes to definite endogenous or exogenous causal factors in an appreciable number of cases. 8. The experimental production of various types of arteriosclerotic lesions in various species by markedly differing chemical and physical agents.

THE SENESCENCE THEORY

The senescence theory of arteriosclerotogenesis assumes that the degenerative and sclerosing changes observed in the arteries are in general the result of physiologic aging processes which may or may not be modified in the individual case by additional vasoactive factors (L. Aschoff, 1933; Bürger and Schlomka; Simms; Hueck; Jores; Liesegang). Askanazy stated that the fully developed atherosclerosis is the senile face of the arteries. This dogma receives one of its main supports from the fact that the general incidence and extent of arteriosclerosis increase with age. Hueck thus noted that all persons between 60

and 70 show senile arterial ectasies and depositions of fat, calcium and hyalin in the vascular walls. Ophüls recorded the following age scale of incidence of arteriosclerosis: 20 to 29 years, 3.5 per cent; 30 to 39 years, 9.25 per cent; 40 to 49 years, 26 per cent; 50 to 59 years, 48 per cent; 60 to 69 years, 78 per cent; above 70 years, 90 per cent. He added, however, that old age did not appear to be the most essential factor and that vascular lesions of senility would likely be diffuse and not patchy.

While the general mortality and morbidity statistics on arteriosclerosis have serious shortcomings that invalidate any precise conclusions as to the extent to which the disease actually occurs and results in illness and death (Sydenstricker), Hesse stated that arteriosclerosis was the cause of death or the main disease in 258 (10.3 per cent) of 2,496 adults on whom autopsies were performed in Leningrad, Russia. Commenting on this observation, he noted that arteriosclerosis is more frequently a cause of death after the age of 40 and occupies first place as the main disease after the age of 60. Anitschkow reported that death among 618 persons over 50 was due to arteriosclerosis in 132, while L. Aschoff found that arteriosclerosis was the main disease in all persons over 65 and, together with hypertension, accounted for 25 per cent of all deaths in those past this age.

The practical significance of these findings is illustrated by a statement of Stieglitz, who quoted figures collected by the United States Census Bureau to the effect that in 1980 persons of 45 and over will constitute 40.4 per cent of the total population and that today there are living in the United States nine million persons over 65 subject to degenerative diseases of the old age type, particularly hypertensive arterial disease and arteriosclerosis.

Important additional support for the senescence theory is derived from the demonstration of physical and histologic changes in the arteries related to the aging process and affecting both large and small vessels. Numerous observations have established the fact that the relative width as well as the circumference of the vascular lumen and the length of the large and medium-sized vessels, particularly the aorta and the arteria pulmonalis, increase with age and that the vascular walls become at the same time thicker (Rössle; Kani; Scheel; Suter; Wilens; Dormanns and Emminger). The excessive longitudinal growth of the arteries, especially of the aorta and of the splenic, coronary and temporal arteries, observed with age gives rise to tortuosities (Schäfer; Springorum; Schmidt; Thiersch; Winkler; Pal; Geigel). Other investigators have shown that these gross changes are accompanied by a progressive reduction in the elasticity of the vessels with age (Wilens; Hass; Krafka) and the development of senile ectasies (Ranke).

Histologic investigations have revealed that there occurs with age a degeneration of the elastic elements (Hass; Bell; Ophüls) characterized, according to Hass, not so much by an actual decrease in the amount of the elastic tissue, which remains nearly constant throughout life, as by a peculiar axial crystallization of the elastic lamellas beginning during the fourth and fifth decades. Later on the lamellas undergo granular disintegration, the development of discontinuities filled with collagenous tissue, and reduction in tensile strength. Wilens noted that with age the elastic fibrils lose their natural undulation and fail to recoil on relaxation as effectively as formerly. Krafka, on the other hand, asserted that the loss of elasticity in the period from 20 to 80 years is almost entirely accounted for by a relaxation of the muscular elastic elements causing a decrease in the distensibility of the aortic wall, while a fibrosis of the muscular media plays only a minor part in this phenomenon. It is, however, a well established fact that with increase of age there occurs a gradual increase of connective tissue in the media of large and small vessels, replacing the atrophying muscle cells (Bell).

Following the diffuse thickening of the intima of the large elastic arteries by the formation of a musculoelastic layer and a subsequent fibroelastic layer beginning during childhood and continuing during the adult period of life (Jores; Koch; Hueck; Lewin; Grünstein; A. Aschoff), there start, according to L. Aschoff, during the fifth decade of life a fibrotic thickening of the intima and a loosening of the binding substance of the elastic membranes of the media. This process is accompanied by an infiltration of the interstices of the inner third of the media with a mucinoid substance and by a fibrosing degeneration of the muscular elements of the media. The internal elastic membrane splits, and a second inner membrane develops, while newly formed elastic fibrils appear in the thickened intima. It has been asserted that this diffuse intimal thickening represents a compensatory reaction to a progressive widening of the vascular lumen resulting from the gradual decrease in the elasticity of the vascular wall brought about by the medial changes (Thoma; Wilens).

Similar structural alterations develop with age in the muscular arteries (coronary arteries [Wolkoff; Cohn; Gross, Epstein and Kugel]; common carotid artery, subclavian artery, com-

mon iliac artery [Grünstein]; renal arteries [Kaufmann; Oppenheim; Oliver; Staemmler]; femoral arteries [A. Aschoff]; mesenteric arteries [Schmiedl]; radial arteries [Hallenberger; Sappington and Cook; Hesse]; splenic artery [Staemmler; Herxheimer; Nakonetschny]; subclavian and axillary arteries [Hesse]; thyroid artery [Abe]; lingual artery [Thiessenhusen]; cerebral arteries [Hackel; Baker; Tuthill; Heubner]; arteries of extremities [Bell]). In this connection it is interesting to note that, according to Cohn, the ramus descendens anterior of the coronary arteries matures earliest, indicating that senescence changes of the coronary arteries affect different branches at different age periods. Similar differences as to time of onset of these changes have been observed for the various parts of the arterial tree (Hesse). This observation has led to the introduction of an auxiliary theory in which it is claimed that different tissues possess distinctly different speeds of aging (Rössle calls this disharmonic aging; Bürger and Schlomka, heterochronic aging). Sappington and Cook, on the other hand, observed that the radial arteries participate to a lesser degree in these senile changes than other arteries, while cutaneous arteries do not exhibit any intimal thickenings (Watanabe).

These are the so-called senile vascular changes which represent in the opinion of the supporters of the senescence theory the basis for the subsequent alterations of the lipoidal, hyaline and calcifying types and thus are an integral and important preparatory part of the arteriosclerotic lesions proper.

The physicochemical reactions in the tissues underlying these morphologic senile changes and their secondary arteriosclerotic sequelae are of the following character, according to L. Aschoff, and Bürger and Schlomka: The colloidal gels composing the cellular and the intercellular matter are in youth finely dispersed hydrates of alkaline reaction. With increasing age they become dehydrated (protoplasmic hysteresis), denser, more coarsely dispersed and more acid (Cowdry; Schmidtmann and Hüttich; Dietrich). During this period processes of precipitation and disintegration associated with the demixture of complex colloidal material favor the formation of deposits. Simultaneously, the mucin content of the vascular wall inceases (Bell; Schultze; Dietrich), and the extracellular collagenous and elastic fibrils and hyaline membranes undergo impregnation and disimpregnation with various chemicals, causing molecular transformations of the cement substances and physical and chemical changes of the elastic substances (L. Aschoff). There are an increase of the nitrogenous substances and an accumulation of waste metabolites, such as calcium and cholesterol, in the aging and dehydrated tissues leading to precipitation of these products. The diffusion processes in such bradytrophic tissues having no vessels of their own depend, moreover, on the presence of large surfaces and decrease therefore with the density of the tissues. The localized nutritive disturbances in the tissues affected by these physicochemical reactions are aggravated by the precipitates of calcium and cholesterol, especially as these are usually located near the vascular lumen. Atherosclerosis, according to these conceptions, is essentially the direct result of physiologic senescing processes of physicochemical nature affecting the vascular tissues and is not the reaction product of alimentary hypercholesteremia or disturbances in cholesterol metabolism (Bürger and Schlomka).

Extensive investigations have shown that these physicochemical and morphologic vascular changes are not related to any appreciable quantitative disturbances in the cholesterol and calcium contents of the blood, as these hematic components are not consistently elevated during old age (Page, Kirk, Lewis and Van Slyke; Greisheimer, Johnson and Ryan; Kirk, Lewis and Thompson; Rafsky and Newman; Parhon and Parhon; Ding and Heckscher; Hunt). The appearance of arteriosclerosis has been connected with a physiologic decrease in function of the thyroid gland during advanced years (Horsley; Vermehren; Lorand; Falta). Vermehren compared senescence with a chronic myxedematous state, while Hogg recently called attention to the degeneration of the thyroid gland in prematurely aging patients. Similar conclusions have been drawn as to the relation between the cessation of the functional activity of the sexual glands and arteriosclerosis, especially as definite vasomotor disturbances are frequently found in women after oophorectomy and menopause and are not infrequently found also in men after castration and during the climacteric (Douglas; McGavack; Dingemanse, Borchardt and Laquer). These phenomena are apparently related to the disturbances in sex hormone metabolism accompanying such changes of senescence. As these responses in the production and excretion of androgen and estrogen in persons at the climacteric and in castrated persons are accompanied by hyperplasia of the adrenal cortex (Koch), a modified activity of the adrenal cortex has been related to the dehydration of the tissues occurring in senescence and in the development of arteriosclerosis. The question whether or not the production of senile vascular changes has a causal connection with the increasing incidence

of high blood pressure in old age as a phenomenon of possibly physiologic nature (Hass; Scheel; Russek; Master and Dack; Master, Marks and Dack; Howell) assumes in this connection a much more prominent position.

The data presented represent the main circumstantial evidence advanced in support of the senescence theory of arteriosclerotogenesis. Against the validity of the conclusions drawn from this evidence the following objections have been raised:

Arteriosclerosis with certain exceptions is a slowly progressive chronic process ending in scar formations like parenchymatous degenerations in other organs. It is for this reason that studies on arteriosclerotogenesis emphasizing the changes found during the senile period of life have only little value, as at such an advanced stage of arterial alteration secondary degenerations, nonspecific cicatricial end products and complex causal influences prevail, obscuring the effects of well defined etiologic agents active during preceding decades. Since senile arterial changes are of diffuse character, while arteriosclerotic lesions are focal in the early stages, the arteriosclerotogenic factors must differ fundamentally in their action from those operative in the development of senescence processes. This basic distinction between the senile and the arteriosclerotic manifestations is not obviated by the allegation that the arteriosclerotogenic effect of mechanical factors in the form of normal strain and stress acts more intensely on certain parts of the vascular tree than on others.

Appreciable arteriosclerosis is not a constant phenomenon in old age. Groddeck found that in 33 per cent of autopsies on persons over 80 years of age only minimal atherosclerotic lesions were observed. Cunningham at autopsy on a man aged 106 observed that the arteries throughout the body were slightly dilated but he saw no sign of atheromatosis and only little loss of elasticity. Humphrey noted that arterial disease was absent in 72 per cent of 824 persons between the ages of 84 and 100 years. Stumpf mentioned the occasional absence of arteriosclerosis in persons of advanced age. Tuthill, studying the changes of the cerebral arteries with age, stated that the divergence of the ages in groups with similar lesions does not suggest that arteriosclerosis is a disease of old age but that it occurs at any time. Boas, commenting on these observations, stated that if arteriosclerosis is a process of aging, early arteriosclerosis is a sign of early aging and that coronary arteriosclerosis in the fifth decade is evidence of an early local senescent change. However, in the opinion of Boas the phenomena of senescence should be encountered with some degree of uniformity in arteries throughout the body and should appear with some degree of regularity and with similar frequency among persons of the two sexes and of different races. This is definitely not the case. Thus, L. Aschoff conceded that arteriolosclerosis is not a disease related to senile changes. This observation applies particularly to the sclerosis of the splenic arterioles which may be found in healthy persons in the first decade of life (Matsuno). Isolated arteriosclerosis, restricted to a small part of the arterial tree, such as the coronary vessels, is of frequent occurrence in relatively early periods of life. The sclerotic and atheromatous involvements, of the aorta and the large elastic arteries, moreover, are often not associated with lesions similarly advanced in extent and degree in the muscular arteries of the extremities or in the organic arteries and arterioles.

It is not admissible that physicochemical and anatomic vascular changes of senescent nature can provide the common basis for both the atheromatous and the fibrosing intimal lesions affecting the large elastic vessels, or for the predominance of the medial calcinosis in the muscular arteries of the extremities, or for the fibrinoid necrotic changes of the medium-sized and small arteries, or for the intimal hyalinosis of the arterioles (Sappington and Horneff). There is, moreover, no consistent relation between the degree and the distribution of senile vascular changes and those of atherosclerosis at any age period (Dormanns and Emminger). Thiersch, Kümmell and Hasenfeld noted, on the other hand, that isolated atherosclerosis of the abdominal arteries occurs without corresponding sclerotic changes in the ascending and cerebral arteries but occurs frequently with considerable sclerosis in the abdominal aorta and in the iliac arteries. Schmidt, commenting on the fibrosing intimal thickenings observed in the tortuous temporal arteries of young persons, stated that such changes do not represent a form of juvenile sclerosis and do not signify that the person affected is predisposed to arteriosclerosis, as the lesions in the tortuous temporal vessels are frequently present and are not associated with arteriosclerotic or atheromatous changes in other arteries.

Coronary arteriosclerosis is in general much less common in women than in men, and thromboangiitis obliterans is a disease only rarely met with in women. Arteriosclerosis is less frequent among Negroes than among white persons (Johnston; Peery and Langsam). The senescence theory is thus entirely inadequate to furnish a plausible explanation for the occurrence of the anatomically widely divergent types of

arteriosclerotic lesions, for the predominant occurrence of the various morphologic kinds of changes in different parts of the arterial tree and for the distinct variations in incidence between the races and the sexes.

Differences in the anatomic structure and topographic distribution of the aortic lesions also cannot be attributed to senescent changes of the vascular reactivity toward cholesterol, as asserted by Leary, who maintained that young arterial tissue reacts to the invasion of lipophages with the formation of atheromas, while old arterial tissue responds with fibrotic lesions and has lost the capacity to dispose rapidly of the cholesterol deposits in the way in which the juvenile tissue is said to be capable.

Additional weighty evidence against the general validity of the senescence theory is supplied by the not infrequent demonstration of local as well as generalized arteriosclerotic, arteriocalcinotic and atherosclerotic lesions in babies, children and young adults (juvenile arteriosclerosis) (Hughes and Perry; Stumpf; Martius; Feyerabend; Dwyer; Clark; Werner; Herzog; Marchand; Benda; Bernhard; Bril and Libmann; Bull; Filatoff and Rachmaninoff; Froboese; Glaser; Rach; Schrötter; Hild; Smyth and Goldman; Shelling and Rausen; Girgensohn; Meyer; Deus; Brown and Richter; Iff; Eisler; Thomasen; Lippincott; Simon; Fremont-Smith; Frothingham; Baggenstoss and Keith; Durante; Jaffé; Bryant and White; Surbeck; Verocay; Johansson; Forrer; Lightwood; Hoelzer; Bernhard; Jamison and Hauser; Hesse; Zinserling; Gerlach; Beitzke; Scheidegger; Bahrdt; Lubarsch; Schlayer; Vollbrecht; Köhler; Huber; Oppenheimer; Oberndorfer; Paechtner; Simnitzki).

It is noteworthy that arteriosclerosis of babies and infants affects growing, not aging, tissue. In some of the cases of juvenile arteriosclerosis the cause of the arterial changes remained undetermined; in others it was related to renal rickets, renal or essential hypertension, vitamin D poisoning, parathyroid hormone poisoning, hypothyroidism, cardiac defects and anomalies, infectious diseases and intrauterine inflammations. In several of these cases the arterial abnormalities were evidently of congenital nature since the affected babies were only two to three days old (Surbeck; Jaffé) or were even of premature birth (8 months), dying a few minutes after delivery (Iff). Mönckeberg reported an incidence of atheromatosis in 51 per cent of men 17 to 45 years old and in 46 per cent of women of this age range. Kohlhaas found typical atherosclerosis in 77.54 per cent of men 20 to 30 years old, and Oberndorfer noted arteriosclerosis as common in persons 20 to 30 years of age. Saltykow confirmed the findings of Kohlhaas.

Attention must be called here to the appearance of the so-called lipoid spots or atherosis of the aorta in babies and children, starting with 3 months of age, as these intimal lipoid imbibitions can scarcely be regarded as senile manifestations but are considered by some observers to be precursors of the atherosclerotic lesions of later life (Zinserling; Schmidtmann; Martius; Stumpf; Kube and Ssolowjew; Lubarsch; Jores; Saltykow). Brief mention may be made in this connection of a statement of Fox as to the apparent absence of degenerative vascular diseases in some species of wild animals at any age, although other animals (cattle) disclose such manifestations at a relatively youthful period of life.

The correlation of endocrine disturbances (senile hypofunction of the thyroid gland; hyperplasia of the adrenal cortex) of the senescence period with the development of arteriosclerosis cannot be considered a well established observation. Such endocrine functional disturbances would seem to favor increased hydration of the tissues rather than the dehydration which plays a significant role in the concepts of the physicochemical changes associated with senescence and its alleged arterial sequelae.

This conclusion is supported by some experimental evidence obtained from studies on the nature of factors controlling longevity and senescence (McCay). This investigator found that rats raised from an early period of life on moderately restricted diets (probably inadequate in vitamin content) with a consequent stunting of growth showed, on one hand, a general and marked prolongation of their average life span and thus a delay and slowing of the physiologic aging processes in comparison with normally and adequately fed rats. They showed, on the other hand, a precocious and extensive calcifying type of arteriosclerosis of the aorta and the coronary and renal arteries. Observations of similar nature and significance were recently made by Hueper during a study of the organs of hairless rats and their haired litter mates which had been exposed over a prolonged period to intense ultraviolet radiation. It was found on that occasion that the haired rats, which have a considerably longer average life span than the hairless litter mates and thus presumably pass through a slower aging cycle (555 days and 365 days, respectively), displayed a much more severe and widespread degenerative and calcifying arterial disease, affecting the aorta and the arteries of the heart, the lungs, the kidneys, the pancreas,

the adrenal glands, the epididymis and the testis, than that observed in the hairless variety. This experimental evidence indicates that the factors controlling senescence and longevity are not identical with those eliciting arteriosclerotic manifestations and that exogenous influences may play an important role in determining the onset and development of these conditions.

Fox made similar observations in regard to the relationship between longevity and arteriosclerosis in wild mammals and birds kept in captivity, as the arteriosclerotic animals lived about twice as long as those dying without vascular lesions. It is, moreover, a well established fact that the experimental production of degenerative and sclerosing vascular disease in animals can be accomplished without regard to the age of the animals.

A large amount of clinical, pathologic and experimental evidence connecting endogenous and exogenous factors with the production and precocious appearance of sclerosing and atheromatous intimal lesions as well as medial degeneration and necroses cannot be reconciled with the senescence theory.

The evidence presented indicates that aging processes which start in some of the arteries soon after birth vary greatly in the time of onset, in the speed of progress and in the degree of development with the different parts of the vascular tree. These diffuse proliferative and atrophic changes in the vascular walls which represent a part of the natural process of aging are distinct in their significance and causation from the unnatural acquired local arteriosclerotic lesions which are often superimposed on them (Tuohy). The nature of some of the senile vascular changes makes it likely, however, that these may play a role in the localization of the arteriosclerotic abnormalities.

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THE MECHANICAL TRAUMA THEORY

Mechanical trauma of the structures of the vascular walls resulting from the presence of exogenous physical forces or of physiologic or pathologic hemodynamic forces is looked on by many investigators (Aschoff; Allbutt; Duguid; Harrison; Leary; Adami; Krafka; Menne, Beeman and Labby) as a principal or an important contributory cause of the development of chronic degenerative arterial disease. Cramer compared the intimal thickenings of the arteries to the occupational calluses on the hands, as the local vascular lesions are the result of local strains caused by the impact of the blood on the wall at certain sites (bifurcations). It is claimed that a continued mechanical strain, affecting especially the sites of vascular fixation (bifurcations) and consisting of such forces as tension, vibration, and shearing between intima and media, cause a loosening of the connective tissue ground substance or a separation of the intima from the media and favor thereby the imbibition in these areas of the lipoid-containing plasma as well as the development of a reactive intimal proliferation. Some investigators have contended that the localization of these lesions depends on mechanical factors of vascular dynamics interfering with the nutrition of restricted areas of the vascular wall and favoring thereby the infiltration of cholesterol through the "stomata" of the endothelial lining into the subintimal tissue (Aschoff; Leary). Intimal herniation resulting from stretching of the fenestrae of the elastic membrane by a physiologic or a pathologic intravascular pressure elicits an irritational intimal proliferation and thus represents the general cause of arteriosclerosis and atheromatosis, in the opinion of Krafka.

Beneke in his studies on the early stage of arteriosclerosis emphasized the etiologic importance of stress and wear and tear. He pointed out that the mechanical stress exerted on the vascular wall in a longitudinal and a transverse direction by the impact of the pulse wave, as well as the stresses operating in an oblique direction through the action of the blood current, affect mainly the connective tissue parts of the walls. While the oblique stress causes primary intimal sclerosis, the longitudinal and transverse stresses elicit, according to Beneke, such reactions only after primary medial malacia has been produced. The primary intimal sclerosis favors secondary deposition of mucinoid and lipoid materials, which may occur, however, also on a primary basis in connection with lipoidosis.

Geigel, as well as Pal, claimed that sudden and marked fluctuations in pulse pressure cause vascular tortuosities by producing excessive longitudinal tensions in the vascular wall. Springorum noted that nodular arteriosclerosis of the splenic artery follows on, and increases in degree with, the tortuosity of the vessel. Albutt assumed that the trauma of a shearing action between intima and media resulting from the rhythmic contractions and dilations of the vascular walls leads ultimately to an intimal proliferation. Aschoff contended that there occurs a loosening of the intimal tissue at the points of fixation due to the mechanical circulatory strain, resulting in an imbibition and swelling of the intimal ground substance. Adami believed that the mechanical strain placed on the media by the circulatory fluctuations causes a weakening of the medial tissues which is reacted to by a hypertrophy of the intima. Duguid's hypothesis asserted that the branches of a vessel act as drags on the main vessel during the systolic lengthening of the vessels, causing splits and chinks and separating the intima from the media, with subsequent thickening of the inner membrane.

Thoma's histomechanical theory as applied to arteriosclerotogenesis resembles in some respects the concept of Adami, as Thoma assumed in his three histomechanical laws that there is a primary weakening of the media (angiomalacia) which results in a widening of the vascular lumen. This development produces a decrease in blood pressure and a slowing in blood current and is reacted to by a contraction of the media. As the angiomalacia prevents a sufficient narrowing of the lumen by muscular contraction, a proliferation of the intima ensues. Thus, the speed of the marginal blood flow controls the width of the vascular lumen and thereby the proliferation and

thickness of the intima by acting on the tension of the tangentially located elastic-muscular intimal tissue. Ranke agreed that such a mechanism may account for diffuse intimal thickenings but not for nodular ones, in the production of which a different mechanism was said to be active. In the opinion of Ranke it is possible that with marked fluctuations in blood pressure persistent crater-like dilatations of the orifices of the intercostal arteries may be produced which exert a shearing influence on these parts of the vascular wall and cause a shifting between the intima and the media in these regions. In response to these mechanically produced local distentions, an irregular fibrous tissue proliferation appears in the intima filling the crater-like excavations and thereby creating protruding intimal thickenings. Fuchs contended that a diffuse type of arteriosclerosis develops in those vessels in which a weak longitudinally stretching force is exerted, while a nodular form appears in the parts that are more strongly stretched longitudinally.

Mechanical factors have been claimed to be active in the localization of arteriosclerotic changes on the posterior aspects of the aortic wall, which is fixed against the spinal column and therefore not as distensible as the anterior aspect (Ranke). Similar conditions seem to exist and are said to be responsible for the especially marked atherosclerotic involvement of the internal carotid artery where it passes through and is fixed to the os petrosum (Albrecht). On the other hand, it is known that those parts of arteries which are subject to frequent passive motion, such as parts located in joint regions (popliteal artery), are exceptionally free from arteriosclerotic and mediocalcinotic lesions (Oberndorfer). Thiessenhusen noted, however, that arteries located in organs which are moved extensively (tongue, extremities) and which are exposed to bending and kinking show frequently an isolated calcinosis of the internal elastic membrane. Wilens, on the other hand, asserted that fixed areas of the aorta lose their elasticity simply through relative disuse or that regenerative or replacement processes are so directed as to maintain the more mobile parts of the aorta in a more elastic condition or that the firmly attached portions are subject to greater stress and strain. Lauda noted, while studying the pressure changes and arteriosclerotic alterations in the meningeal arteries, that the pressure changes involve the vascular aspect adjacent to the bone and start in the outer part of the media with degeneration, homogenization and calcification, followed by intimal thickening, while the arteriosclerotic lesions begin in the intima and extend outward. There is no causal relation between the two phenomena. Mechanical factors alone therefore do not cause, in the opinion of Lauda, arteriosclerosis.

Exogenous mechanical vascular injury by contusion of the arterial wall, which is important in peace as well as in war times, has been considered as a potential factor in the production of arteriosclerosis. Such local vascular traumas occur in persons involved in mine disasters and in the collapse of dugouts and air raid shelters by explosive action, where whole limbs are impounded by falling masses of stone, concrete or lumber and their vessels compressed, and in persons sustaining tangential bullet wounds to arterial vessels (Küttner; Schmincke; Reichardt; Thiem; Fränkel). Such tangential shots exert a shearing force on the vascular tissues by pushing the inner parts of the walls across an unyielding blood column and causing thereby, through an excessive stretching of the vessel, tears and hemorrhages in the intima and the media. While such injuries usually result in the development of thromboses, occasionally they may give rise to locally restricted arteriosclerotic lesions (Schmincke; Fränkel; Reichart; Thiem) characterized by a fibroelastic proliferation of the intima, intimal calcification, sometimes complicated by mural thrombi, and irregular medial muscular proliferations.

The role of mechanical trauma in the development of arteriosclerotic lesions was investigated experimentally by numerous workers (Malkoff; d'Anna; Schilling; Lange; Andriewitsch; Fabris; Sumikawa; Hildebrandt; Jores; Borst and Enderlen; Ziegler; Jaffé, Willis and Bachem; Malyschew; Farmachidis; Ssolowjew) and by various methods, such as crushing of the vascular wall with a forceps (traumatic crush arteriosclerosis [Ziegler]), dissection of the adventitia, sheathing of the vascular wall in paraffin or application of silver nitrate, zinc chloride, oil of turpentine or thermocautery to the outside of the vascular wall. The primary result of these manipulations was usually necrosis of the media, sometimes with preservation of the elastic elements (after mild cauterization), followed by the appearance of granulation tissue in the media, extending from the intima, and a regenerative fibroblastic thickening of the intima.

In spite of the many elaborate and painstaking investigations as to the primary causal role of mechanical factors in the production of arteriosclerosis, the evidence presented indicates that such physiologic or pathologic influences seem to play, if any, a merely minor and secondary role in the general development and localization of degenerative arterial disease. The allegations

made in this respect neglect to take proper consideration of the fact that conditions accompanied by an abnormal mechanical strain of the vascular wall, such as overdistention or overcontraction caused by fluctuations in hydrostatic pressure or in vascular tonicity, exert also a definite and appreciable influence on the blood circulation in the vasa vasorum and therefore on the nutrition and the permeability of the vascular walls. The local accidental and experimental traumatic arterial lesions are not comparable to those of ordinary arteriosclerosis in developmental and morphologic respects (White and Glendy; Kessler).

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THE TOXIN THEORY

Some investigators favor the conception that certain substances of bacterial origin or of endogenous or exogenous chemical nature exert a specific and direct cytotoxic effect on the vascular wall and thereby give rise to atherosclerotic, arteriosclerotic and arteriocalcinotic lesions.

The theory of the infectious genesis of arteriosclerosis, championed originally by Virchow and supported later in a modified form by Klotz, Saltykow, and others, assumes that bacteriotoxins present in the blood injure the intima and prepare it for the subsequent atheromatous changes by increasing its permeability to the cholesterol and fats contained in the plasma.

From an analysis of 500 autopsies Ophüls concluded that chronic arterial disease occurs frequently and early in persons with preceding infectious diseases and that both arteriosclerosis and hypertension are sequelae of toxic action, as no definite relations were demonstrable between vascular disease and hypertension. Mönckeberg considered aortic atherosis in children an acute reaction to infectious diseases and atherosclerosis etiologically related to chronic infectious diseases. Faber, Schmidtmann and Saltykow emphasized the importance of tuberculosis in this respect. Wiesel, Wiesner and von Simnitzky advocated an infectious origin (diphtheria, typhoid, pneumonia, influenza, scarlet fever, measles, septicemia) of intimal and medial degenerations in childhood. Similar observations were made by Beitzke, Wail and Stoerk and Epstein. While Stumpf could not establish definite relations in regard to the causal role of acute infectious disease, he came to the conclusion that chronic infectious diseases, such as tuberculosis, are apparently involved in the production of arteriosclerosis in young persons. Scharpff, on the other hand, was able to substantiate the findings of Wiesner to only a limited degree. The observations of Wiesel and Wiesner on the etiologic relation of juvenile arteriosclerosis to infectious diseases were preceded by those made by several French and English workers, who reported the

occurrence of medial degenerations, situated particularly in the ascending aorta, in children dying from infectious diseases (Huchard; Brouardel; Landouzy and Siredey; Thoinot; Barié; Korcynski; Thérèse; Roger, Gouget and Boinet; Cowan and others). Verocay described the occurrence of nonspecific extensive mediocalcinosis in many arteries and of endarteritic changes in a 6 month old girl with congenital syphilis.

The medial changes attributed to the toxic action of infectious diseases and found in many arteries, including the aorta and the coronary vessels, consist in general of a hydropic swelling and a proliferation of connective tissue in the media, a granular degeneration of the elastic fibrils and a calcification of the internal elastic membrane, leaving as end products hyaline scars. Actual necroses of the muscle cells of the media are rare. The intima is usually much less intensely affected. It may show cushion-like cellular thickenings with new formation of elastic fibrils. An accumulation of lipoidal material is seen occasionally in the hydropically swollen intima. Scharpff noted that degenerative changes of the elastic tissue (granular disintegration, fragmentation, tears) occur as a main feature in association with diphtheria, typhoid, pneumonia and influenza.

Menten and King by injecting sublethal amounts of diphtheria toxin into guinea pigs kept on a diet low in ascorbic acid obtained diffuse hyperplastic intimal thickenings and medial fibrosis in the arteries and arterioles of the lungs, the liver, the spleen and the kidneys; the arteries of the brain and the heart remained intact. The elastic tissue degenerated first, showing variability in stainability, loss of wavy contour, clumping and disintegration. Other bacterial toxins (Pneumococcus, Staphylococcus, Bacillus coli, Bacillus typhosus, Salmonella enteritidis, Streptococcus) injected intravenously elicited similar arterial lesions in vitamin C–deficient guinea pig. Similar experimental results with diphtheria toxin were recorded by Duff. Saltykow reported intimal lipoidal degenerations and medial calcifications in rabbits similarly treated but kept on an unphysiologic milk diet, which was shown later to be responsible for the intimal lipoidotic changes produced. Winternitz and LeCompte injected suspensions of various bacteria (Staphylococcus aureus, Bacillus pyocyaneous, Streptococcus viridans, Actinomyces) into the adventitia of the carotid, jugular and femoral arteries of goats and observed the appearance of intimal nodules or plaques having a hyaline or a fibrous structure covering a media and an adventitia with inflammatory reactions. Starokadomsky observed the presence of medial degenerations in the aorta of rabbits given injections of a vaccine made from Staph. aureus. According to Klotz, typhoid vaccine injected into rabbits caused thickening of the intima and degeneration of the inner media, whereas the introduction of diphtheria toxin elicited medial necrosis and calcification. Sweeney and Smith were, on the other hand, unsuccessful in producing any arterial lesions in rats by injecting suspensions of Staph. aureus. This indicates that a species-specific reactivity to the toxin plays an important role.

Similar claims of a direct toxic action on vascular walls were made in connection with the arteriosclerotogenic effect of several vasotonic agents. It was contended that epinephrine exerts its arteriosclerotogenic effect by a direct toxic action on the media (Stief and Tokay; Waterman; Ziegler; Schirokogoroff; Heusner; d'Amato; Lissauer; Toropow; Braun; Sturli). An identical mechanism is present, according to some observers, in the arteriosclerotogenic action of nicotine (Beneke) as well as in that of the vasotonic-hypercalcemic agents, parathyroid hormone and vitamin D.

It is obvious that the toxin theory is not generally applicable, as there are other mechanisms by which arteriosclerotic lesions, especially those of the intimal and atheromatous types, are produced. The etiologic significance of infectious diseases in the development of these disorders is moreover disputed by Ribbert and Lange. MacCallum concluded from an analysis of the available clinical, pathologic and experimental evidence that there is little support in favor of the idea that acute or chronic infections play a great part in the genesis of arteriosclerosis and atheromatosis. Zinserling arrived at a similar judgment in regard to the alleged arteriosclerotogenic role of tuberculosis, dysentery and scarlet fever. It is noteworthy that the vasotonic effect of bacteriotoxins has not found the proper consideration as an arteriosclerotogenic factor in the evaluations of the relationship between infectious diseases and arteriosclerosis.

Similar doubts must be entertained concerning the direct medionecrotic action of certain vasotonic agents, as there are a large number of additional agents of that type (tyramine, digitalis, ephedrine, physostigmine, barium chloride, lead and others) eliciting identical arteriosclerotic lesions which are the result not of a primary cytotoxic mechanism but of ischemia due to vasoconstriction. The absence of medionecrosis of the pulmonary artery in animals given injections of epinephrine or nicotine is an additional factor which is not in harmony with the concept that

arteriosclerotogenic agents exert a direct toxic effect on vascular walls. The refractoriness of other species than the rabbit in reacting with arterial lesions to the introduction of bacterial toxins supports this contention, as different species vary greatly in their reactivity to vasotonic agents.

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THE ANOXEMIA THEORY

It is apparent from an analysis of the available biologic, pathologic and experimental data dealing with the genesis of degenerative and sclerosing arterial diseases that a relatively large number of chemical and physical agents are capable of eliciting arteriosclerotic lesions of various kinds and in different sites and distributions in man and experimental animals. Some of them are of endogenous nature, such as hormones, amino acids, amines and other metabolites. Others are of exogenous origin and represent environmental influences of dietary, medicinal, occupational, habitual, bacterial, parasitic and chemoallergic nature. A classification of these etiologic factors on the basis of the different causative mechanisms by which they act on the vascular walls demonstrates the polyetiologic character of arteriosclerosis (table 1).

It is the contention of the anoxemia theory of arteriosclerotogenesis that the common fundamental action through which the various types of causal agents and their different causal mechanisms affect the vascular walls is represented by a severe and short or a moderate and prolonged but frequently recurring or persistent interference with the oxidative metabolism and nutrition of the vascular wall. The validity of this concept on which the classification of the causal agents is based is supported by evidence obtained from an analysis of the degenerative organic lesions found in association with the vascular changes. These organic degenerative manifestations are elicited by an appreciable number of the aforementioned agents in the brain, the heart, the stomach, the blood, the thyroid gland and the testes, where they are caused by a local anoxemia related to the arteriosclerotogenic mechanism.

Softenings in the basal ganglions of the brain, giving rise in many instances to the symptom complex of parkinsonism, are observed in poisonings by carbon monoxide, carbon disulfide, cyanides, lead, manganese and mercury and are attributable to functional vascular, circulatory or hematic anoxemic disturbances. Ischemic degenerations, necroses and fibroses of the myocardium are characteristic of poisonings with epinephrine, nicotine, digitalis glucosides, parathyroid hormone, vitamin D, histamine, nitrites, carbon monoxide, carbon disulfide, reduced oxygen pressure and excessive physical labor. Peptic ulcers

TABLE 1.—*Classification of Etiologic Factors of Spontaneous and Experimental Arteriosclerosis*

I. Vasotonia
  A. Hypotonia followed by stagnant anoxemia and increased permeability of the relaxed vascular walls through excessive slowing of the blood flow.
    1. Endogenous agents: histamine, acetylcholine, orthostatic vasomotor insufficiency, hypoadrenalism, hypothyroidism, hypopituitarism.
    2. Exogenous agents: nitrates and nitrites, cyanides, carbon monoxide, barbiturates, reduced atmospheric oxygen pressure, arsenic, mercury, manganese, traumatic shock.
  B. Hypertonia followed by constrictive ischemic anoxemia of the vascular tissues as a result of the compression of the vasa vasorum and by reduced permeability of the contracted vascular wall, which hinders the movement of tissue fluids and the action of diffusion processes.
    1. Endogenous agents: epinephrine; hormones from the adrenal cortex, the posterior lobe of the pituitary gland, the thyroid gland and the parathyroid glands; angiotonine; tyrosine; tyramine; guanidine.
    2. Exogenous agents: synthetic epinephrine, desoxycorticosterone, ephedrine and derivatives, ergotine, physostigmine, hydrastine, nicotine, digitalis glucosides, S-methyl isothiourea, vitamin D, calcium salts, chemicals producing acidosis and hypercalcemia (ammonium chloride, ammonium hydroxide, calcium phosphate and others), barium chloride, mercury bichloride, uranium, iodine, chemoallergies, cold, solarization, vibration, trauma, cutting of depressor nerves, psychic strain.

II. Intravascular Hydrostatic Pressure.
  A. Decreased hydrostatic pressure (local or general) followed by ischemic anoxemia of the vascular wall as a result of the reduction or cessation of blood supply.
    1. Endogenous mechanisms: disuse and senile involution by changes in normal circulation (umbilical artery, omphalomesenteric arteries, ductus arteriosus, uterine and ovarian arteries).
    2. Exogenous mechanisms: proximal and distal parts of ligated arteries, distal part of artery in arteriovenous aneurysm, arteries located in scar tissue (radiodermatitis, floor of chronic gastric ulcer, perinephritic tissue), distal part of arteries with proximal spastic contractions (renal arterioles in nephrosclerosis), scleroderma.
  B. Increased hydrostatic pressure (local or general) followed by ischemic anoxemia as a result of the compression of the vasa vasorum against the inelastic adventitia and by mechanical overextension of the contractile and elastic elements in the vascular wall.
    1. Endogenous mechanisms: Local: congenital cardiac and vascular abnormalities of the pulmonary circulation (open foramen ovale, septal defects, transposition of large vessels, open ductus arteriosus, mitral stenosis, congenital hypoplasia of the small pulmonary arteries or of pulmonary veins), coarctation of the aorta, sites of arterial bifurcations. General: plethora.
    2. Exogenous mechanisms: Local: excessive physical labor, traumatic arteriovenous aneurysm, pulmonary fibrosis of pneumoconiotic or infectious origin, pulmonary emphysema, pulmonary bilharziasis, abnormal static condition (gravity forces in posture (standing), centrifugal and accelerating forces in flying), chronic pulmonary edema in oxygen and phosgene poisoning, consumption of excessive amounts of liquids and general circulatory failure.

III. Colloidal plasmatic instability resulting in the formation of films and precipitates on the intima and thereby impairment of the exchange of gases and nutritive substances across the interface between blood and intima as well as decreased permeability of the vascular wall.
  A. Lipoidal plasmatic disturbances lowering the stability of the cholesterol in solution by changes in the quantitative or the qualitative cholesterol content.
    1. Endogenous disturbances: hyperlipoidemia in diabetes mellitus, hypothyroidism, essential xanthomatosis, glycogenosis, pregnancy, Gaucher's disease, psoriasis.
    2. Exogenous disturbances: (*a*) Hyperlipoidemia with excessive dietary lipoid intake, lipoid nephrosis, starvation, carbon disulfide poisoning, goitrogenic substances (sulfaguanidine, thiourea derivatives, thiocyanates). (*b*) Agents either increasing the precipitability of cholesterol in solution or lowering its stability (saponin).
  B. Carbohydratic plasmatic disturbances.
    1. Endogenous disturbances: glycogenosis.
    2. Exogenous disturbances: polyvinylosis, methyl cellulosis, pectinosis, arabinosis.
  C. Proteinic plasmatic disturbances.
    1. Endogenous disturbances: amyloidosis, hyperglobulinemia.
    2. Exogenous disturbances: allergic hyperglobulinemia, experimental proteinoses (gelatin, ovalbumin, serum azoproteins).

IV. Hematic anoxemia.
  A. Agents producing inert hemoglobin derivatives (carbon monoxide hemoglobin, sulfhemoglobin and others): carbon monoxide, sulfonamide compounds, nitrites.
  B. Agents producing disturbances in the oxygen-carbon dioxide balance: reduced atmospheric oxygen pressure, oxygen poisoning (hyperoxemic hypoxidosis).

of the stomach, on the basis of local ischemic vasospasm or stagnant anoxemia, are found in connection with poisonings by lead, manganese, mercury, carbon monoxide, carbon disulfide, cyanides and nicotine. Chronic anoxemia of various types and genesis is responsible for the degeneration of the spermatogenic epithelium of the testes in exposures to reduced atmospheric oxygen pressure (chronic mountain sickness) and in poisonings by lead, mercury, manganese, carbon monoxide, carbon disulfide, nitrites, nicotine, Evans blue and diabetes mellitus. Anoxemic erythrocytoses are seen under the influence of reduced atmospheric oxygen pressure and after chronic exposures to carbon monoxide, nitrites, lead, epinephrine, amphetamine, ephedrine, posterior pituitary hormone, cyanides, S-methyl isothiourea, lead, manganese, pulmonary fibrosis and cardiac anomalies interfering with pulmonary circulation and oxygenation. Mention may finally be made of the fact that an anatomically and, with some substances, also functionally hyperactive thyroid gland, an organ playing an important role in the oxygen metabolism of the body, is found after poisonings with carbon monoxide, mercury, lead, manganese, cyanides, thiourea and sulfonamide compounds.

The existence of several groups of causative agents having distinct causative mechanisms indicates that the anatomic character of the vascular lesions elicited by them must reflect these differences. It is evident, moreover, that such a relationship is not agent specific but group specific and is manifested not only in the morphologic character of the early lesion but also in the type of its subsequent development. The intensity and the duration of action of an arteriosclerotogenic agent exert, on the other hand, a distinct influence on the structural kind and site of the ensuing reaction within the vascular wall and on its distribution within the vascular tree. The type and the extent of the topographic response depend, moreover, on the special vasoactive properties of a particular agent and on the degree and the time of its action.

It is obvious that such relatively uncomplicated causal and developmental conditions prevail mainly in children with arteriosclerosis and in those young persons and young adult persons who either suffer from endogenous diseases with well defined vascular action mechanisms or are exposed to environmental and particularly occupational influences operating on the tonus and the metabolism of the vascular walls, the circulation or the physicochemical composition of the blood. The arteriosclerosis of old persons, on the other hand, very likely is in most instances a complex product brought about by the simultaneous or the successive action of several

arteriosclerotogenic agents to which they were subjected in the course of life. The anatomic types of arteriosclerotic lesions which may be encountered either alone or in various combinations in an artery or in different parts of the arterial system are listed in table 2.

VASOTONIA: A. HYPOTONIA FOLLOWED BY STAGNATION ANOXEMIA; AGENTS AND INFLUENCES PRODUCING IT

Certain agents cause relaxation of the muscular elements in the vascular walls and thereby distention of the vascular lumens, with hypotension and reduction in the speed of blood flow. Such functional vascular and circulatory

TABLE 2.—*Anatomic Types of Arteriosclerotic Lesions*

1. Intimal mucinosis
2. Intimal hyalinosis
3. Intimal fibrosis
4. Intimal elastosis
5. Intimal lipoidosis (atheromatosis)
6. Intimal calcinosis (ossification)
7. Medial mucinosis
8. Medial fibrosis and hyalinosis
9. Medial amyloidosis
10. Medial calcinosis (ossification and cartilage formation)
11. Medial fibrinoid necrosis
12. Medial cystic degeneration
13. Degenerative and necrotizing fibrinoid angiopathy associated with inflammatory and granulomatous or thrombosing components of probably allergic nature (periarteritis nodosa, thromboangiitis obliterans, malignant nephrosclerosis, rheumatic angiitis, temporal arteritis)

reactions result in stagnant anoxemia, which in turn injures the endothelium, increases the permeability of the vascular wall and thereby its imbibition of stagnating plasmatic matter, and impairs the oxygenation and the nutrition of its cellular elements.

Acute and severe hypotonic episodes are apt to elicit the most severe metabolic disturbances in the media of the large arteries, because the inner third of the media normally depends entirely on diffusion processes for its nourishment and gas exchange, the rate of which is reduced in stagnant anoxemia, as the rate is controlled by the potential created by the type of blood and the speed of blood flow. The outer two thirds, which receive oxygen and nutritive substances from the blood circulating through the vasa vasorum, suffer in acute hypotonia under similar metabolic conditions, as stasis develops in the blood flow of these small nutritive vessels under the influence of the markedly lowered blood pressure. These anoxemic effects in the media are expressed morphologically as acute degenerations and necroses.

Prolonged and moderate hypotonia, on the other hand, causes less abrupt and serious anoxemic disturbances and elicits therefore anatomic reactions of a more complex degenerative and proliferative nature affecting all layers of the vascular wall.

Vasodilating depressors are either products of endogenous metabolism, such as histamine, acetylcholine and its derivatives (mecholyl and the like), or factors of exogenous origin, such as inorganic and organic nitrites and nitrates (sodium nitrite, amyl nitrite, glyceryl trinitrate, erythrol tetranitrate, ethylene glycol dinitrate, mannitol hexanitrate and others), methyl xanthines (caffeine, theobromine, theophylline, aminophylline), ethyl alcohol, barbiturates, carbon monoxide, cyanides, atropine, bacteriotoxins, arsenic, manganese, mercury, aromatic amines, hydrocarbons, reduced atmospheric oxygen pressure and heat. Many toxic chemicals to which people are accidentally or occupationally exposed may cause hypotonic hypotension (Dally; Hueper [1940]; Foulger and Fleming). Mention must be made in this connection of the hypotonus resulting from impaired vasomotor reactivity to changes in posture (gravitational or orthostatic hypotension) and of the essential abdominal hypotonus occurring particularly in women with weak abdominal walls which causes circulatory disturbances through the accumulation of blood in the splanchnic organs (Klotz). Acute hypotonic episodes are moreover a characteristic phenomenon of traumatic shock. Vascular hypotonicity on an endocrine basis is observed in hypopituitarism, hypoadrenalism and hypothyroidism (Kerley and Lorenze; Kylin; Martini and Pierach; Cadbury; Fossier; Barach). While some of the aforementioned agents when given in moderate doses display a more or less transitory vasopressor effect, by acting either simultaneously on the heart (caffeine) or by containing a pressor component (acetylcholine), all of them are vasodepressants when present in excessive amounts and may cause persistent hypotension when acting over prolonged periods (barbiturates, nitrites).

The relative rarity of chronic pathologic hypotensive states in comparison with hypertensive conditions may account in part for the fact that little attention has been paid heretofore to the possibility that regionary or generalized vascular hypotonia may be involved in the production of arterial degenerative disease (Hesse; Faber; Külbs). It is, however, a well established observation that inordinately prolonged and intensive relaxation of the arterial walls with resulting fall in blood pressure and slowing of the blood flow is followed by proliferation of the intima and degeneration of the media with gradual obliteration of the vascular lumen (Ceelen; Fischer-Wasels; Plesch; Lange).

ENDOGENOUS AGENTS.—*Histamine.*—Hueper and Ichniowski recently studied the aorta and large and small arteries of dogs subjected to lethal or sublethal histamine shock. The acute vascular reactions in dogs which died within the first sixteen hours after shock were characterized by mucinoid or plasmatic imbibition and swelling of the aortic media, local appearance of albuminoid masses in the intima obliterating the demarcation between the intima and the media of the aorta, occasional hemorrhage into the media and, in the case of some myocardial arteries and of arterioles in the neighborhood of acute peptic ulcers of the stomach, extensive swelling and homogenization of the media.

The delayed reactions in dogs which survived the shock for one to three weeks consisted of extensive focal degenerations and hyalinizations of the aortic media often associated with the presence of multiple small cysts of liquefaction necrosis. These were filled with cellular debris or a homogeneous albuminous matter. In such regions the walls of the vasa vasorum were sometimes thickened and homogeneous. Calcifications of the internal elastic membrane of the aorta and of small cerebral vessels were occasionally present.

It is significant that similar anatomic changes (edema of the media, especially around vasa vasorum, disappearance of elastin and muscular tissue, mucoid-cystic degeneration) of the cystic medial type were noted in the human aorta following burn shock, in the production of which a substance is apparently active which displays pharmacologic properties similar to or identical with those possessed by histamine (Günther; Zinck; Meessen). These aortic lesions resembled closely those described by observers as idiopathic cystic medionecrosis of the aorta or as disseminated medionecrosis of the aorta, which has given rise in many instances to so-called spontaneous rupture of the base of the aorta. (Erdheim; Gsell; Cellina; Weise; Furno; Zimmerman; Wolff; Eck; Harrison; Wenger; Levinson; Rottino; Rottino and Poppiti; Roberts; Castellaneta; Orsos-Debrecen; Oppenheimer; Moritz; Finkensieper; Neubürger; Günther).

In rabbits given repeated injections of small doses of histamine over a prolonged period there were first swelling and plasmatic infiltration of the walls of the small- and medium-sized arteries (myocardial, pulmonary, cerebral) with clumping of the nuclei. The pulmonary arteries had a swollen and loosened media and local intimal thickenings. In more advanced stages of chronic histamine poisoning the media of the myocardial arteries was replaced by connective tissue (Meessen; Heinlein; Rühl; Spiegel-Adolf).

Acetylcholine.—Similar sclerotic lesions (necroses and calcifications) were observed in the myocardial and pulmonary arteries of rabbits given repeated injections of acetylcholine (Hall, Ettinger and Banting; Heinlein) and were attributed to dilatation of the arterioles, lowering of the blood pressure, slowing of the heart action and reduced speed of blood flow causing stagnant hypoxemia. Similar experimental studies of Horswell on dogs failed to demonstrate any lesions except some slight medial thickenings of the coronary arteries.

Anaphylactic Shock.—Meesen recorded swelling of myocardial arteriolar walls and replacement of the medial muscularis by fibrous tissue in rabbits subjected to anaphylactic shock due to injection of serum.

Orthostatic Shock.—Similar hypotonic fibrosing medial changes were noted in the coronary arteries of rabbits exposed repeatedly to orthostatic or gravitational shock by suspension in a vertical position (Meessen; Eppinger). Meessen, commenting on these experimental conditions and observations, compared them to those in man during fainting and in orthostatic collapse, in which similar electrocardiographic reactions have been recorded, reflecting hypoxemia resulting from maldistribution of blood. Meessen felt that peripheral circulatory collapse has a much more serious significance than has been suspected.

Anoxia.—Büchner and Luft observed degenerative and calcinotic lesions in the aortic media of rabbits exposed to an atmosphere of reduced oxygen pressure. Thorner and Lewy saw fibrosing medial changes in the cerebral arteries of cats after these had been subjected repeatedly to anoxia. Campbell noted thickening of the pulmonary arterioles in animals kept for several weeks at a low barometric pressure. These observations are in a way parallel to an observation of Hurtado in a man living at 4,500 meters of altitude who had pulmonary arterial sclerosis and pulmonary fibrosis. Loewy also commented on the presence of circulatory disturbances, such as those manifested in the presence of drumstick fingers, among the natives of the high regions of the Andes. Koelsch mentioned that at high altitudes the blood pressure is lowered owing to the reduction in heart output and the action of the vasodilators.

These observations are of great practical importance because of the demands which flying at high altitudes makes on the vascular system through the necessity of compensating for anox-

emia or oxygen debt incident to other causes. Meessen noted that so far there are available no observations in man that hypoxemia causes changes in large arteries but that the changes in cerebral vessels in carbon monoxide poisoning suggest such relations. The actuality of such connections, which are suspected also by Thorner and Lewy, is further supported by Overhof's report of the presence of hypoxemic symmetric softenings of the globus pallidus and the putamen and of mediocalcinosis associated with thickening and local calcifications of the intima of the medium-sized and small cerebral vessels in a man with severe secondary anemia (hemoglobin content 19 per cent). It is uncertain whether or not the fatal coronary arteriosclerosis and thrombosis associated with atherosclerosis of the aortic arch of a pilot 27 years old described by White is an example of such a mechanism.

Koelsch summarized the situation on this matter in 1932 as follows: "It is not possible to define a definite, strongly characteristic professional ailment. The injuries to the heart and vascular system are not sufficiently characteristic to permit of their being isolated as specific professional ailments." It is hoped that the studies of aviation medicine undertaken in these days are sufficiently extensive and adequate for reaching a final decision on this problem, especially as aviators are likely to become exposed to several additional arteriosclerotogenic agents (carbon monoxide, lead, excessive hydrostatic hypotension and hypertension, oxygen poisoning).

Exogenous Agents.—*Nitrates and Nitrites.*—Glyceryl trinitrate and ethylene glycol dinitrate are used in the production of explosives such as dynamite, cordite and blasting gelatin. Most cases of occupational acute or chronic poisoning with these compounds occur, therefore, in the manufacture of explosives. The medicinal use of various organic nitrocompounds has led to a large number of chronic poisonings and to some that were fatal. In other instances the poisonings were accidental, homicidal or suicidal (Rabinowitch). Recent experimental investigations on chronic nitrite poisoning of young rats, which were subjected to increasing amounts of erythrol tetranitrate for a period of five to seven months, showed that in an appreciable percentage of the animals extensive arteriosclerotic lesions developed in various organs at an extraordinarily early age (Hueper and Landsberg). These lesions consisted of medial degenerations of a hyalinizing, necrotizing and calcifying type, as well as intimal thickenings and perivascular fibrosis, affecting the arteries of the brain, the heart, the lungs, the kidneys and the testes. Identical arterial lesions were found in dogs exposed to contact with glyceryl trinitrate for several months. It is noteworthy that similar vascular changes (coronary arteriosclerosis, medial degeneration and intimal thickenings of myocardial arterioles and medial degeneration and calcification of cerebral arteries, accompanied sometimes by extensive perivascular fibrosis or accumulation of glia cells and brown pigment, arteriolar sclerosis of the renal vessels and other changes) have been observed in chemical workers exposed to nitrites and showing during life the symptoms of chronic nitrite poisoning (excessively low blood pressure, attacks of angina pectoris, bradycardia or tachycardia, passive congestion of internal organs, indigestion, diarrhea, mental deterioration and other signs). Sudden death occurs often at a relatively early period of adult life with the symptoms of coronary thrombosis or cerebral paralysis (Meixner and Mayrhofer; Fischer; Löwy; Laws; Ebright; Robert; Schulz, and others). It is significant that an exposure to two other agents causing vascular hypotension, alcohol and humid heat, aggravate considerably the symptoms of nitrite poisoning or may even set off such acute circulatory collapse in nitrite workers.

Commenting on the dynamics of the arterial changes observed in experimental and occupational nitrite poisoning, Hueper and Landsberg pointed out that nitrites cause, by a relaxation of the walls of the peripheral arterioles with the resultant drop in blood pressure and the slowing of the blood flow, a state of chronic passive congestion and stagnant hypoxemia. The conclusion drawn from this evidence was that the excessive dilatation of the vascular walls resulting from a prolonged effect of nitrites causes partial compression of the vasa vasorum and that the untoward effect produced by this condition on the nutrition of the vascular wall, especially its inner third, is aggravated by the undue slowing of the blood flow and by the pathologic lowering of the blood pressure. This combination of factors impairing the oxygenation, nutritive exchange and discharge of waste metabolites of the vascular tissues leads ultimately to development of degenerative changes in the vascular walls, affecting particularly the arterial vessels of those organs (brain, heart) most readily responding to the nitrites.

Carbon Monoxide.—Acute and chronic carbon monoxide poisoning is one of the most frequent industrial poisonings of accidental or occupational nature. It is characterized by vaso-

dilatation and hypotension affecting particularly the vessels of the brain. The slowing of the blood flow leads to stasis and perivascular hemorrhages in the brain and the heart. The anatomic vascular effects associated with carbon monoxide poisoning, especially the chronic form, are of significance in regard to the causal dynamics responsible for arteriosclerotic changes, as they are similar to those following the acute and severe action of various arteriosclerotogenic agents, hypotonic as well as hypertonic. These changes, usually limited to the small and medium-sized cerebral vessels, are as follows: perivascular edema; vascular dilatation, congestion and thrombosis; edema and swelling of the intima; endarteritic intimal proliferations, and medial hyalinizations and calcifications, the last-mentioned lesions occurring as early as two days after the poisoning. These lesions have been observed in man (Poelchen; Aschoff; Rube; Herzog; Lhermitte; Hsü and Cheng; Forbes, Cobb and Fremont-Smith; Staemmler and Parade; Petri; Cramer; Geipel; Wohlwill; Sibelius; Eros and Priestman; McConnell and Spiller, and others) and in experimental animals (Semerak and Bacon; von Braunmühl; Sayers, Chornyak and Yant; Yant, Chornyak, Schrenk, Patty and Sayers, and others). While myocardial necroses, hemorrhages and fibroses are relatively often seen in carbon monoxide poisoning, hyalinization of the media of the myocardial vessels or coronary arteriosclerosis is apparently infrequent (Gey; Hedinger).

Arsenic.—Acute arsenic poisoning is characterized by paretic vasodilatation, congestion, hypotension and degeneration of the vascular walls (Tscherkess) and occasionally phenomena like those of Raynaud's disease. Chronic atrophic acrodermatitis caused by occupational, environmental, medicinal or accidental chronic exposure to arsenical compounds and resulting in several cases in gangrene of the extremities has been attributed to toxic paralysis of the vasomotor nerves (Geyer; Zinny; Strauss; Kraetzer; Dürck; Kötzing; Kren; Butzengeiger). The histologic examination of the small arteries of the involved subcutaneous areas showed endarteritis and medial degenerations without calcifications (Bering; Heinz; Petri; Freise; Kötzing). The gangrenous reaction in the extremities observed in several cases may be looked on as the equivalent of the focal anoxemic myocardial and cerebral necrosis produced by those agents which exert their main vasodilating effects on the cerebral and coronary vessels.

Aromatic Hydrocarbons.—In this connection the hypotensive state observed in workers who inhale toxic amounts of vapors from benzene, xylene and aniline is noteworthy. The occurrence of hemorrhages, medial arterial necroses and calcifications and other signs of pronounced arteriosclerosis in relatively young workers exposed to these agents has been noted repeatedly (Hayhurst and Neiswander; Columbus; Petri; Griesbach; Gehnau; Hirsch; Koelsch).

Manganese.—Lewy and Tiefenbach, as well as Grünstein and Popowa, observed swelling and degeneration of the endothelium and fibrous thickening of the walls of the small cerebral arteries in rabbits fed manganates. Kan-Jin-Nan reported the development of medial necroses and calcifications in the aortas of rabbits poisoned intravenously with manganese salts. Schmidtmann raised the question whether the degenerative changes observed in the nervous system of the manganese worker are caused by vascular changes of the mentioned type. Wright noted that this metal is capable of producing sclerotic lesions in the arteries of man. Voss found in the vessels accompanying the ischiadic nerve of a man who had died from chronic manganism proliferation of the endothelium and loosening of the vascular wall with vacuolation and severe damage to the elastic tissue and thickening of the collagenous fibrils. Similar changes were present in the vessels of the spinal cord and meningeal membranes, but they were infrequent in the cerebral vessels.

Mercury.—Chronic mercury poisoning in man and animals has been shown to be associated with certain vascular changes, especially in the brain, in the internal organs and in the extremities. Guiljarowsky and Winokuroff observed in man endothelial proliferation and thickening of the walls of the small arteries of the liver, the peripheral nerves and the brain. Schenken and Hausmann reported obliterative vascular lesions of endarteritic type in the mesenteric vessels of 3 patients with chronic mercury poisoning. The subintimal connective tissue was markedly proliferated, and hyalinization was present in the walls of some vessels. The presence of similar obliterative vascular changes in the arteries of the legs was suspected by Fellinger and Schweitzer in 3 cases in which chronic mercury poisoning led to gangrenous processes in the legs. Rivela noted in dogs subjected to alkyl mercury poisoning thickenings of the walls of the small and medium-sized cerebral vessels, a finding I can confirm from my own observations in animals. Philosophon by treating rabbits with mercury bichloride obtained necrotic and calcified foci in the media and intimal thickening of the ascending aorta.

Bacteriotoxins.—Mention has already been made in connection with the discussion of the toxin theory that degenerative and fibrosing changes in the vascular walls of large and small vessels were observed in association with acute and chronic infectious diseases. It was pointed out that a direct and specific vasotoxic effect of bacteriotoxins appeared to be unlikely and that apparently the well recognized hypotonic vascular effect exerted by these agents was involved in the production of the lesions (Borst). In support of this concept attention is called to the edematous imbibition of the media in persons who have died from diseases accompanied by circulatory failure (Wiesel; Segre and Kellner). This relatively acute reaction, occurring apparently during the preagonal stage, may be related to the hydropic swelling of the intima and media and the hyaline and fibrotic foci subsequent to the necrosis and atrophy of the muscular and elastic elements reported by Wiesel, Wiesner, Stumpf and others in the media of large and small arteries of children who had suffered from acute infectious diseases and seen by Stoerk and Epstein, Scharpff and others in adults who had died with acute infectious diseases, such as typhoid, typhus, influenza, pneumonia, diphtheria and septicemia. Various authors (Chiari; Kugel and Epstein; Beitzke; Klinge and Vaubel; Gray and Aitken; Breitenecker) have called attention to the presence of medial necrosis and cyst formation in the pulmonary artery in connection with rheumatic fever, similar to those found in the aortic media in association with this disease, as well as with typhoid, influenza and scarlet fever, and resembling the changes reported by Gsell as idiopathic cystic medionecrosis of the aorta and attributed by him to the action of poisons. These lesions start as mucoid imbibition of the media, with formation of small cavities filled with mucoid material in the connective tissue. The surrounding elastic and muscular tissue is thereby compressed and undergoes degenerative changes. In addition to these nonspecific changes in rheumatic fever there are those of specific rheumatic nature. The lesions heal with the formation of scars.

Physical or Chemical Agents Producing Traumatic Vasoparesis.—A paretic vasodilatation produced by cutting of or mechanical or chemical injury to nerves has been used by several investigators in attempts to obtain degenerative and sclerosing lesions in arteries supplying the area innervated by the injured nerve (Vulpian; Giovanni; Fraenkel; von Czyhlarz and Helbing; Jores; Lewaschew; Lapinsky). Vulpian cut the ischiadic nerve in dogs, rabbits and guinea pigs and found that the small arteries in the corresponding muscles were dilated and showed mild adventitial hyperplasia. Giovanni noted yellow "atheromatous" spots in the intima of the descending aorta in dogs after having cut the thoracic sympathetic nerves several months previously. Bervoets cut the ischiadic nerves of rabbits and observed soon afterward atrophy of the muscle cells in the media and endothelial intimal proliferation of endarteritic type in the arteries receiving their innervation from the cut ischiadic nerves. Fraenkel recorded the presence of thickened, tortuous arteries with medial hypertrophy and arteritic intimal proliferation in dogs and rabbits three months after the cutting of the ischiadic nerves. Lapinsky resected the cervical sympathetic ganglions in rabbits and observed after six weeks that the carotid arteries had thickened walls, while the smaller arteries showed typical endarteritic lesions, their lumens being narrowed or obliterated by proliferated endothelial cells, while the muscular media was atrophic and the adventitia was hyperplastic. Von Czyhlarz and Helbing cut the ischiadic nerves of rabbits and observed similar changes, which were, however, situated mainly in arteries near ulcerations. Sternberg, on the other hand, performed the same operation on rabbits with negative results as to arterial lesions. Similar failures were reported by Jores, who cut the cervical ganglions of rabbits. He considered the arterial changes observed the result of inflammatory processes in nearby ulcerated regions.

Lewaschew elicited vasodilatation by drawing threads soaked with hydrochloric acid or sulfuric acid through the ischiadic nerves of young dogs and found the vessels of the legs dilated, the media atrophic and, sometimes, the intima thickened.

While Jores and also Marchand were skeptical as to the causal significance of nerve injury in the production of this neurotic angiosclerosis, Saltykow conceded that such injuries may cause first medial muscular hyperplasia followed by collagenous sclerosis of the media and fibrous thickening of the intima. Fraenkel suggested on the basis of the experimental evidence that the occurrence of precocious angioscleroses in persons with severe nervous disorders (tabes dorsalis, progressive paralysis, polyneuritis) and with noninflammatory trophic changes of the skin and muscles might be etiologically related to functional vascular abnormalities resulting from primary injuries to nerve tissue.

Although these observations do not establish reliably the occurrence of angioneurotic arteriosclerosis, attention may be called to the fact that the sympathectomy performed for the relief of

vasospastic conditions in the lower extremities usually is of only transitory benefit. It stands to reason that a recurrence may become manifest whenever the newly created functional vasoneurotic abnormalities have caused anatomic vascular lesions of the type described. The simultaneous development of testicular degenerations after extensive sympathetic ganglionectomies in the abdominal region supplies additional suggestive evidence that severe anoxemic vascular reactions may follow such surgical procedures (Hueper).

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(To Be Continued)

Obituaries

WILLIAM GEORGE MacCALLUM, M.D.

1874-1944

Dr. William George MacCallum was born in Dunnville, Ontario, Canada, on April 18, 1874. He was the second of four children, having an elder and a younger sister, and a younger brother, John Bruce MacCallum, whose brilliant carreer in medical research was cut short by his death from tuberculosis at the age of 30.[1] The mother, Florence Octavia Eakins, was born in Sparta, Ontario. She was an accomplished pianist and singer, and from her, doubtless, Dr. MacCallum acquired his deep and lifelong love of music. His father, George Alexander MacCallum, born in Stouffville, Ontario, was a general practitioner with an active practice in the countryside surrounding Dunnville. Later, he served as medical superintendent of two hospitals for the insane in Ontario, and when the family moved to New York after Dr. MacCallum had become professor of pathology at Columbia University, his father, then about 70 years of age, became pathologist of the Bronx Zoo and of the Aquarium, and, at the suggestion of the younger MacCallum, he entered on a study of the worm parasites of captive animals—a subject which he pursued eagerly and to which he made numerous contributions. As a youth, Dr. MacCallum often rode with his father on visits to patients, and helped him at times during operations by administering ether and by "purifying the air of the room" with the Lister phenol spray.

Dr. MacCallum was taught at home until he was 9 years of age. He then attended public school, and at the early age of 15 passed the entrance examinations at the University of Toronto with First Class Honours. He entered the University at 16 years of age, completing in four years the requirements for the degree of Bachelor of Arts and, in addition, a sufficient number of medical courses to enable him to enter the second year class of the Johns Hopkins Medical School, in the company of the small group who, in the preceding year, had been the first students to be admitted to the newly opened school. In 1897, at the age of 23, he was graduated at the head of his class. After a year spent in a rotating internship in the Johns Hopkins Hospital, he applied, without success, for a place on Osler's staff. Dr. Welch then offered him an assistantship in pathology, which he accepted. He progressed rapidly in rank, becoming associate professor of pathology in 1902. In 1905 he initiated a pioneering course in pathologic physiology, and in 1908 he was made professor of pathologic physiology and lecturer in forensic medicine. The following year he succeeded Dr. Prudden as professor of pathology at Columbia University, where he remained until 1917, when he returned to the Johns Hopkins University to succeed Dr. Welch as Baxley professor of pathology.

Dr. MacCallum's interest in scientific investigation early manifested itself. While an undergraduate student at the University of Toronto he was awarded a gold medal for a paper on worm parasites, and it is significant that one of his most important contributions was made at home during the summer vacation following his graduation from medical school. This was the discovery that the flagellated form of the malarial parasite represents the sperm cell, a fact which provided the key to the solution of the life cycle of the parasite. Young MacCallum reported his discovery at a medical meeting in Toronto, at which Lord Lister presided. Some years later Sir Ronald Ross said about this discovery by the young medical student: "I have ever since felt disgraced as a man of science!" For Ross had erroneously interpreted the sperm cell wiggling into the penetrated female cell as being a flagellated spore trying to escape from it.

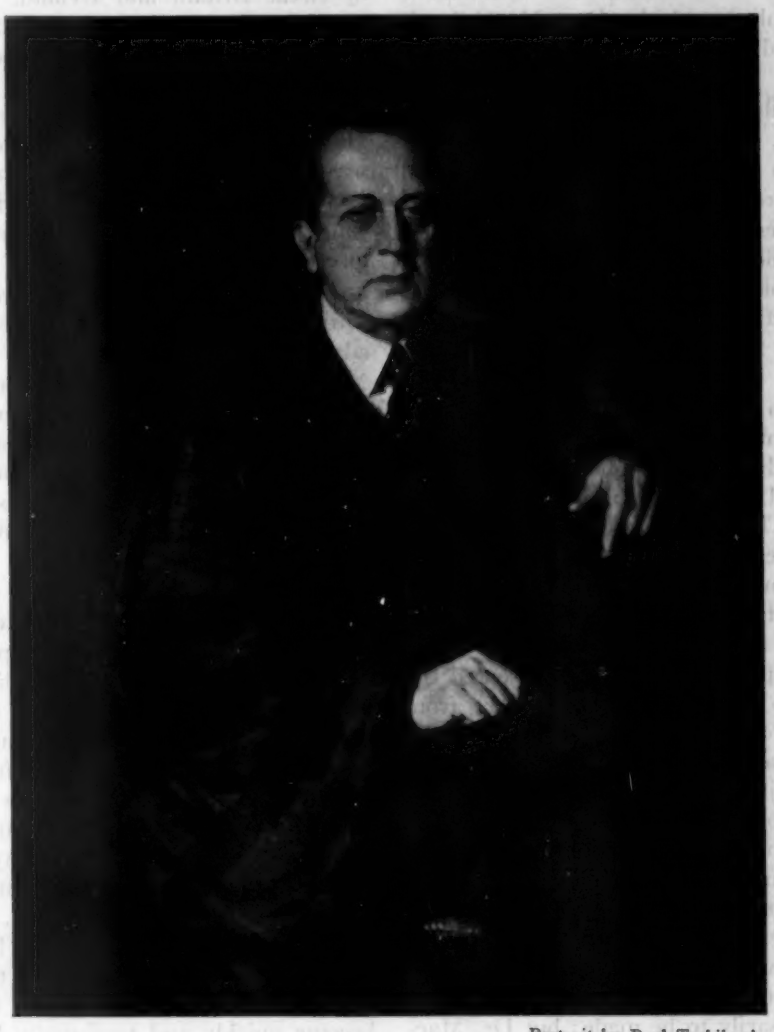
His next contribution of major importance was published several years later, when he was 28 years of age. This was the demonstration that the lymphatic vessels constitute a closed system with continuous walls, instead of having openings in communication with the tissue spaces, as was widely believed at that time. The far reaching significance of this fact in relation to the physiology and the pathology of the tissue fluids and the lymph needs no comment. This paper was followed by one in which he clearly demonstrated for the first time the mechanism of the absorption of granular materials and red blood cells from the peritoneal cavity.

In 1905, at the age of 31, Dr. MacCallum published the first of the series of his studies which revealed the function of the parathyroid

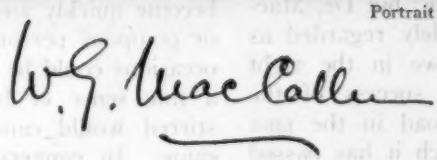
1. A biography of this brother, by Archibald Malloch, has been published under the title "Short Years."

glands. By means of beautifully contrived experiments, in which Dr. Carl Voegtlin was an active collaborator, it was shown that the amount of calcium in the blood is maintained at a normal level by the activity of these minute glands; that insufficiency of parathyroid secretion leads to a loss of calcium from the blood; that the normal amount of circulating calcium is necessary to temper the excitability of the motor nerves; that the fatal tetany which results from insufficiency of parathyroid secretion is due to the diminution of the calcium in the blood, and, finally, that the symptoms of tetany can be made to disappear at once by the administration of calcium. This investigation was one of the most important of the pioneering studies on the functions of the glands of internal secretion.

Another fundamental study, which he published in 1909 at the age of 35, established the fact that the function of the pancreas in relation to carbohydrate metabolism and diabetes is localized in the islands of Langerhans. This has been suspected from the morphologic observations of Opie and others but had remained unproved and uncertain until Dr. MacCallum showed that when the pancreatic duct is ligated, all of the pancreatic glandular tissue except the islands undergoes atrophy and disappears, but diabetes



Portrait by Paul Trebilcock.



WILLIAM GEORGE MacCALLUM, M.D.
1874-1944

does not occur. If, however, the remaining film of tissue containing only the islands is extirpated, diabetes follows immediately. The procedure (ligation of the duct) employed by Dr. MacCallum in order to destroy the acinous tissue while leaving the islands intact was later adopted by Banting and Best in their successful attempt to extract from the islands the antidiabetic hormone (insulin) which Dr. MacCallum's experiments had shown to be secreted by those cells.

Other contributions to pathologic anatomy and physiology, which cannot be outlined here, are contained in his bibliography of one hundred and seventy-three papers, which include biographic sketches and studies in medical history, a subject in which he had an enduring interest. In his superb biography of Dr. W. H. Halsted one can read between the lines much of his own attitude toward science, toward life and toward his fellow man.

No discussion of his contributions could stop short of the mention of that work which has had so wide an influence throughout the English-speaking world, namely, his "Textbook of Pathology." This book, which appeared in 1916, was written in a lucid and engaging style, and with an inquiring, critical attitude made sound by a rich personal experience with the subject matter. It was a landmark in the history of textbooks of pathology, for it represented the first attempt to treat the entire subject from the standpoint of etiology. In this book the attempt was made to present the effects that each form of injury, each cause of disease, produces in the whole body, instead of following the traditional method of cataloguing all of the heterogeneous and unrelated injuries that can affect each separate organ. Of course, because of the incomplete state of knowledge, it was impossible to write of all morbid conditions from a strictly etiologic standpoint, and compromises had necessarily to be made; but Dr. MacCallum's attempt has been widely regarded as a fundamentally important move in the right direction. The extraordinary success of the book in this country and abroad in the past twenty-eight years, during which it has passed through seven editions, attests plainly enough the approval which his method of treatment of the subject aroused.

While at Columbia he played an important role in the progressive reform that abolished the political coroner system in New York, and introduced the much superior system through which the examiner of medicolegal cases must be a skilled pathologist, selected from the civil service list by competitive examination; in Baltimore he was associated with a similar reform.

In recognition of his scientific attainments he was made a member of the National Academy of Sciences in 1921. He was also an honorary fellow of the Royal Society of Medicine, London, 1918; honorary member, Pathological Society of Great Britain and Ireland, 1940; honorary member, Societas Medicorum Sverana, Stockholm, 1918; corresponding member, Societas Regia Medicorum, Budapest, 1938; honorary member, Societé d'Endocrinologie, Paris, 1939; Hon. D. Sc., University of Toronto, 1927. He was a member of numerous American medical societies but, save for the Association of American Physicians, he rarely attended society meetings.

The last entry in a year to year outline of his activities that he kept reads: "1941. War advanced throughout Europe. Have been in Marburg for several days, confusion of pronunciation, etc., also in country for days. Going to Winter Park, Florida." At Winter Park he suffered a stroke that paralyzed the right side and robbed him of speech. He remained bedridden thereafter until his death on Feb. 3, 1944.

Dr. MacCallum's nature was of a complexity that renders it impossible to sketch his personality satisfactorily in a few simple strokes. He was a man of strong likes and dislikes, and contradictory emotional forces were not infrequently at play. He lived simply, though he was responsive to beautiful and tasteful surroundings and had a gourmet's appreciation of the pleasures of the table. He had wide cultural interests. He greatly enjoyed good conversation on all manner of subjects save politics and metaphysics, and was a delightful, sparkling and stimulating conversationalist. Though he would converse eagerly for hours with those who could ably cross swords with his keen mind, he would become quickly and profoundly bored with dull or pompous persons, and his boredom on such occasions could be appallingly evident. He had a fine sense of humor which when properly stirred would cause him to laugh until tears came. In conversation he was always at his best with a single companion or with one or two intimates, for, in spite of his acquired ease among people, he was basically a shy and sensitive person. His fastidiousness in personal contacts, and his aloofness that bordered at times on the brusque, were attributable in part to his inherent shyness. "I was never a good mixer," he once said. "I scarcely got to know my classmates at Toronto." He shrank from the familiarity that most men find agreeable, and

would actually wince on the rare occasions when some venturesome colleague would call him Bill.

He remained a bachelor, but he thoroughly appreciated the society of attractive and intelligent women, not a few of whom remained his devoted admirers throughout the years, being drawn to him by his personal charm, his courtly, thoughtful ways, his splendid and artistically sensitive mind and, possibly in the instances in which their attitude was a motherly one, by their intuitive recognition of his ordinarily concealed shyness. He had a charming and disarming way with children that immediately won their confidence. He himself possessed a marked degree of filial piety, and his concern over his aging parents was deep, unremitting and touching.

Though possessing an excellent physique, he cared nothing for sports, whether as a participant or as a spectator. He was very fond of travel, and his trips to far away lands were usually enlivened by the performance of autopsies on persons who died with lesions that were extreme or with diseases unfamiliar to this clime, and by the search for new parasites in tropical animals. He would return laden with notes and interesting pathologic material. On his last visit to the Orient he wrote from Singapore in a discouraged vein:

> There are none of the wonderful things I used to see. The commercial exploitation of 606 or something like it has ruined the syphilis. There is no malaria. I've done cases of tuberculosis of the lungs, epithelioma of the oesophagus, etc., etc., and I doubt whether I'll have anything worth bringing home. I'm afraid it will be just the same in Rangoon. There are no worm parasites any more either. I've found one hookworm, and before everybody had all these things. But what is the good in coming out here to do autopsies on cases of carcinoma of the stomach and tuberculous peritonitis!

But soon he would be describing vividly the strange landscapes, golden pagodas and women in bright dresses smoking cheroots of huge size. He took many photographs of the scenes of his travels, and these he had made into lantern slides on his return to exhibit to small groups of friends, with delightful running comments.

His absorbing interest in pathology was carried into all sorts of situations. He was continually on the alert for evidences of disease in people on the streets or in public conveyances. Sometimes he would place a section under his microscope, ask for a diagnosis and after a discussion of the lesion he would smilingly say: "I saw a curious speck in a filet mignon last week at the Blank's dinner party, and I cut it out, slipped it into my pocket and had a section made." Hostesses who learned of this penchant have confessed to a degree of nervousness during the main dinner course when he was a guest.

He loved science, and his scientific ideals were of the purest. He hated dogmatism and cant in whatever relation and was himself completely free from those blights of the spirit. He was a teacher of great simplicity and charm, and he deeply enjoyed his contacts with the medical students. His relations with most of the members of his staff were not close. It was as though he hesitated to intrude himself into their activities, for he always seemed pleased when they came into his laboratory to consult him. In their turn, they felt hesitant about intruding on him. They were given the broadest freedom of action, but this freedom was tempered by the unpremeditated, constant example of his own high scientific ideals, his continually inquiring attitude, his freedom from dogmatism, and his devotion to the accurate and meticulous study of the manifestations of disease. The influence of his attitude, which pervaded the department, had an enduring effect on most of those who became members of his staff, and few have worked in his department who have not acquired from his example a deeper appreciation of the pleasures and satisfactions of a free spirit of inquiry disciplined by a high regard for accuracy of thought and observation.

ARNOLD R. RICH.

Notes and News

Appointments.—Ann G. Kuttner, lecturer in bacteriology at the Harvard Medical School, has been appointed bacteriologist of the Mary Imogene Bassett Hospital in Cooperstown, N. Y.

Valy Menkin has been appointed assistant professor of pathology in Duke University, Durham, N. C.

Francis D. Gunn, associate professor of pathology at the Northwestern University Medical School, has been appointed professor and head of the department of pathology of the University of Utah School of Medicine.

Otto Schales, director of the clinical laboratories of Peter Bent Brigham Hospital, Boston, has been appointed director of chemical research of the Ochsner Foundation and director of the biochemical laboratory at the Ochsner Clinic, New Orleans. The chemical laboratories of the Ochsner Foundation will specialize in research on the therapeutic aspects of medical enzymology.

Charles H. Kellaway, director of the Walter and Eliza Hall Institute of Research in Pathology and Medicine of the Royal Melbourne Hospital, Australia, has been appointed director of the Wellcome Foundation Research Laboratories in England and in the United States. His headquarters will be in London.

Ivan C. Hall, formerly professor of bacteriology and public health in the University of Colorado, has been appointed professor of bacteriology in New York Medical College.

In the University of Texas, Galveston, Harry H. Sweets Jr. has been promoted to associate professor of pathology and Norman D. Schofield to assistant professor of pathology.

Deaths.—Louis A. Julianelle, bacteriologist, chairman of the division of infectious diseases of the Public Health Research Institute of the City of New York, died on August 12. He was 49 years old.

John Shaw Dunn, professor of pathology in the University of Glasgow, hospital pathologist, investigator of renal physiology and the discoverer of alloxan diabetes, died June 10 at the age of 61.

Lawrence J. Rhea, professor of pathology, McGill University, Montreal, Canada, and director of the pathologic laboratory of the Montreal General Hospital, died July 3, aged 67.

American Board of Pathology.—The present members are: A. H. Sanford, Rochester, Minn., president; F. H. Lamb, Davenport, Iowa, vice president; F. W. Hartman, Detroit, Mich., secretary; R. A. Moore, St. Louis, assistant secretary; N. C. Foot, New York; F. W. Sunderman, Philadelphia; James B. McNaught, San Francisco; Shields Warren, Boston; and Major R. Philip Custer, Medical Corps, Army of the United States.

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